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EARLY RESTORATIVE REHABILITATION OF CHILDREN AND ADOLESCENTS WITH AMELOGENESIS IMPERFECTA

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Early restorative rehabilitation of children and adolescents with Amelogenesis imperfecta
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My deepest gratitude to all the patients that participated in these studies, to those brave patients who had the courage to try a new, untested treatment, and to those of you who open-heartedly shared your thoughts and problems about living with AI.

What is right is not always popular and what is popular is not always right

-Albert Einstein

ABSTRACT

Amelogenesis imperfecta (AI) is a rare, genetically determined defect in enamel mineralization. Patients with (AI) can present with rapid tooth loss or fractures of enamel and dental sensitivity as well as alterations in enamel thickness, color, and shape. These factors may compromise esthetic appearance and masticatory function. Existing treatment recommendations suggest using resin composite restorations until adulthood, although such restorations have a limited longevity.

The main aims of this thesis were to compare oral health and the quality and longevity of dental restorations in a group of young patients with AI to a control group. Second, this work aimed to compare the quality and longevity of two crown types, Procera and IPS e.max Press, in adolescents and young adults with AI and to document any adverse events. A third aim was to study oral health-related quality of life (OHRQoL), dental fear, and dental beliefs before and after early prosthetic crown therapy. Finally, we aimed to explore the experiences and perceptions of adolescents and young adults living with AI and receiving early prosthetic therapy.

Study I examined the oral health and the quality and longevity of dental restorations in 82 patients with AI, 40 boys and 42 girls, 6 to 25 years old (mean age 14.5±4.3 years) and a control group matched in age, gender and area of residence. Annual mean number of dental visits in the AI group was 2.9±1.7 compared to 1.9±1.2 in the control group ($p<0.001$). The number of decayed, missing and filled surfaces was 8.1±15.6 in the AI group compared to 1.0±2.0 in the control group ($p<0.001$). The longevity of dental restorations was significantly lower in the patients with AI, with 24.7±35.1% of the AI group requiring replacement of fillings during the observation period compared to 9.2±23.7% in the control group ($p<0.001$). Patients with hypomineralized/hypomatured AI had restorations of shorter longevity than those with hypoplastic AI ($p<0.01$). Porcelain crowns had significantly longer survival than composite resin materials in the AI group ($p<0.001$).

Study II included 27 patients with AI 11 to 22 years of age and in need of crown therapy in a randomized controlled trial using a split-mouth technique. After placing 119 Procera crowns and 108 IPS e.max Press crowns following randomization, we recorded longevity, quality, adverse events, and tooth sensitivity. After 2 years, 97% of the crowns in both groups had excellent or acceptable quality. We found no significant differences in quality between

Procera and IPS e.max Press crowns. Tooth sensitivity decreased significantly after crown therapy ($p<0.001$). Endodontic complications occurred in 3% of crowns.

Study III asked patients to complete three questionnaires measuring oral health related quality of life (OHRQoL) (OHIP-14), dental fear (CFSS-DS), and dental beliefs (DBS-R). We included 69 patients with AI, 6 to 25 years old, 33 males and 36 females (mean age 14.5±4.3) as well as healthy controls (n=80), patients with cleft lip and palate (CLP; n=30), and patients with molar incisor hypomineralization (MIH; n=39). All groups were matched in age and gender, and all but the CLP group in socioeconomic area. Patients with severe AI between the ages of 9 and 22 received crown therapy and completed the questionnaires both before and after therapy. OHIP-14 scores were significantly higher among patients with AI (7.0±6.7), MIH (6.8±7.6) and CLP (13.6±12.1) than among healthy controls (1.4±2.4) ($p<0.001$). After crown therapy, OHIP-14 scores in patients with severe AI decreased significantly from 7.8±6.1 to 3.0±4.8 indicating an improved OHRQoL. Early prosthetic therapy did not increase dental fear or negative attitudes toward dental treatment.

In Study IV, seven patients with severe AI aged 16 to 23 years who underwent porcelain crown therapy participated in one-on-one interviews. The interviews followed a topic guide consisting of open-ended questions related to experiences of having AI. We analyzed transcripts from the interviews using thematic analysis. The analysis process identified three main themes: Disturbances in daily life, Managing disturbances, and Normalization of daily life. Experiences included severe pain and sensitivity problems, feelings of embarrassment and shame, and dealing with dental staff who lacked knowledge and understanding of their condition. The patients described strategies to manage their disturbances, reduce pain when eating or drinking, and for meeting other people. After definitive treatment with porcelain crown therapy, they described feeling like a “normal” patient.

These results show that the quality of resin composite restorations in patients with AI is of inferior quality compared to controls. We also found the longevity of resin composite restorations to be shorter than for controls and that prosthetic crown therapy had significantly better quality and longevity than resin composite restorations in patients with AI. Resin composite restorations cannot be recommended for patients with severe forms of AI. After 2 years 97% of the crowns of both Procera and IPS e.max Press crowns had excellent or acceptable quality and no significant difference between the two crown types were found. Crown therapy also resulted in decreased sensitivity problems in young AI patients. We found

it possible to perform crown therapy without adverse effects in young patients with AI and concluded that early permanent crown therapy can be recommended in patients showing severe forms of AI. Patients with AI rated their OHRQoL lower than healthy controls but improved significantly after crown therapy. Extensive therapy did not increase dental fear or negative attitudes towards dentistry. It is evident that orofacial appearance and orofacial pain are factors that need to be addressed and taken into account in the treatment plan. Patients with AI described a profound effects of AI in daily life with severe pain and sensitivity problems and feelings of embarrassment. After definitive treatment with porcelain crown therapy, they described feeling like a “normal” person. Patients with AI were met with lack of knowledge and lack of understanding of their situation in dental care. Continuing education on rare conditions is important as well early referral if the situation cannot be handled in general dentistry.

LIST OF SCIENTIFIC PAPERS

I. Pousette-Lundgren G, Dahllöf G. Outcome of restorative treatment in young patients with amelogenesis imperfecta. A cross-sectional, retrospective study. J Dent. 2014;42:1382-9. Erratum in: J Dent. 2015;43:295.

II. Pousette-Lundgren G, Trulsson M, Morling Vestlund GI, Dahllöf G. A randomized controlled trial of crown therapy in young individuals with amelogenesis imperfecta. J Dent Res 2015:94:1041-7.

III. Pousette-Lundgren G, Karsten A, Dahllöf G. Oral health-related quality of life before and after crown therapy in young patients with amelogenesis imperfecta. Health Qual Life Outcomes. 2015;submitted

IV. Pousette-Lundgren G, Wickström A, Hasselblad T, Dahllöf G. Amelogenesis imperfecta and early restorative crown therapy: an interview study with adolescents and young adults on their experiences. In manuscript

CONTENTS

LIST OF ABBREVIATIONS

AI	Amelogenesis imperfecta
AMBN	Ameloblastin gene
AMELX	Amelogenin X linked gene
AMELY	Amelogenin Y linked gene
AMTN	Amelotin
CDA	California Dental Association
CFSS-DS	Children's fear survey schedule-dental subscale
CLP	Cleft lip and palate
C-ODIP	Child oral impacts on daily performances
COHIP	Child oral health impact profile
CPQ	Child perceptions questionnaire
DBS-R	Dental belief survey - revised version
DEJ	Dentin-enamel junction
DMFS	Decayed missing and filled surfaces
DSPP	Dentin sialophosphoprotein
ENAM	Enamel–producing gene
ES	Effect size
FAM20A	Family with sequence similarity 20, member A
FAM83H	Family with sequence similarity 83, member H gene
GBI	Gingival bleeding index
KLK4	Kallikrein-related peptidase
MIH	Molar incisor hypomineralization
MMP20	Matrix metalloproteinase-20 (Enamelysin) producing gene
MPa	Megapascal
OHIP-14	Oral health impact profile -14
OHRQoL	Oral health related quality of life
PDS	Public dental service
PROM	Patient reported outcome
VAS	Visual analogue scale

INTRODUCTION

Amelogenesis imperfecta (AI) is a genetically determined enamel defect. A variety of conditions of abnormal enamel formation are included in this collective term. AI is characterized by heterogeneity in its clinical manifestations, histological appearance, and genetic pattern. The condition can vary in expression, usually affecting the entire dentition and the need for restorations (Aldred and Crawford, 1995). The phenotype of hypoplastic AI shows quantitative deficiencies and the hypomineralized/hypomatured AI qualitative insufficiency. In the most severely affected patients, teeth can exhibit rapid loss or fractures of enamel, alterations in enamel thickness, color and shape. Several problems are associated with AI, as rapid wear, hypersensitivity, masticatory function problems, gingivitis, frequent replacement of restorations and lifelong extensive restorative care (Coffield et al., 2005). These tooth defects also cause sensitivity problems in the teeth causing problems when eating, chewing and facing cold air as well as problems when having dental treatments. The appearance of teeth is also a burden to the patient affecting self-confidence and leads to avoidance of social contacts.

In one of the first published reports AI was described as "faulty enamel" by Spokes 1890 and referred as hereditary brown teeth (Spokes, 1890). Later AI was subdivided into hypoplastic AI and hypocalcified AI (Weinmann et al., 1945). However AI is not a "new" disorder. An early example of hypoplastic form of AI was diagnosed in a Homo erectus girl found in Ethiopia, dated 1.5 Million years ago (Zilberman et al., 2004). Neither is it an exclusive human disorder, it has been described in poodle dogs (Mannerfelt and Lindgren, 2009), cattle (Cranwell and Schock, 2011) and mice (Li et al., 2013).

Prevalence

The prevalence varies between 1:14 000 (Witkop, 1957), in a population in the state of Michigan, USA, to 1:700 in the county of Västerbotten, Sweden (Bäckman and Holm, 1986). The hypoplastic form of AI is more common (73%), than the hypomatured form in the Swedish study, while the hypomineralized form was more common in USA. Inhabitants in the County of Västerbotten and the County of Dalarna have been stationary over time. The two counties have an agricultural tradition and are low-income regions. The societies of today are more open and the youths are more prone to move for education and job opportunities.

As AI is of genetic origin and the young patients mows more today, one have to expect the differences in prevalence will change in Sweden.

Tooth development

Understanding how teeth develop can help us understand how the disturbances and phenotypes of AI develop as well as the problems for the patient and the possibilities for making long-lasting restorations.

The tooth developing process starts when areas of basal cells of oral embryonic ectoderm proliferate, leading to the formation of a primary epithelial band. This band invades the underlying ectomesenchyme along the future dental arches. The dental lamina serves as a primordium for the ectodermal portion of the deciduous teeth, and the permanent teeth develops from a lingual extension opposite to the enamel organ of each deciduous tooth. Along the dental lamina ectodermal cells multiply to little knots, expanding into the underlying mesenchyme. Each little knot is the beginning of a tooth bud. The transition from the bud stage to cap stage begins with the epithelial bud invaginates at its tip in the cap stage (Fig. 1). The epithelium grows down at the flanks and mesenchyme cells, surrounded by the epithelium forms the dental papilla (Thesleff. and Juuri., 2012). During the bell stage the germ grows and the shape of the tooth crown becomes evident. Secondary enamel knots, from epithelial cells, aggregates and determines the location of the cusps. The tooth germ is organized in three parts; the enamel organ, the dental papilla and the follicle.

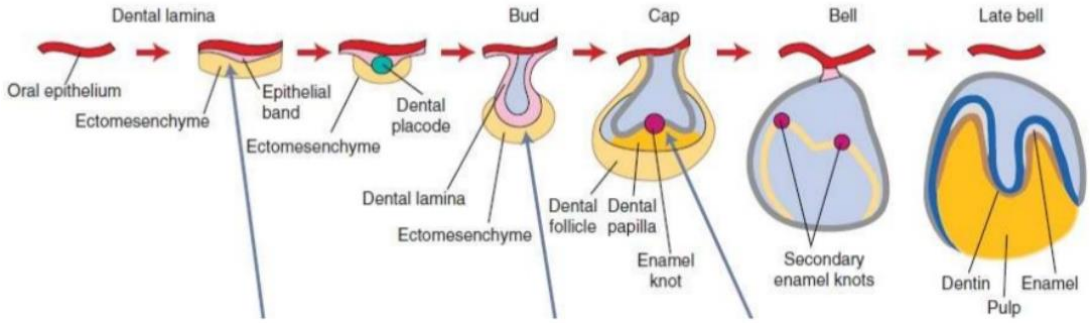


Figure 1. Tooth development illustrated from oral epithelium to late bell stage. Figure from www.slideshare.net/dinow1/tooth-development-part-2?related=13 by Muhammad Awadine

Odontoblasts differentiate first and secrete a collagen-rich pre-dentin matrix directly beneath the epithelial-derived basal lamina (Hu et al., 2007). Dentin and enamel formation take place simultaneously, and both processes start along a line that will become the dentin-enamel

junction (DEJ), enamel on the outer side and dentin in the inner side of the DEJ (Simmer and Hu, 2001). That gives enamel is of ectodermal origin and dentin and other tooth structures of the associated mesenchyme. Dentin mineralization does not occur until the basement membrane material is removed. Differentiating ameloblasts start expressing enamel proteins even before the basal lamina disintegrates.

Enamel formation

Enamel is built up of tightly packed crystallites that comprise 87% of its volume and 95% of its weight. Mature enamel includes less than 1% organic material. Enamel crystals are extremely long relative to their thickness and are highly oriented (Simmer and Hu, 2001). The ectodermal origin of enamel explains why enamel defects are not associated with dentin defects. A highly specialized process regulated at the molecular level and involving numerous genes and their products result in the final enamel. These processes involve numerous developmental and regulatory pathways that could lead to abnormal enamel development and pathology if not sufficient. Ameloblasts play two key roles during amelogenesis. They secrete the four major enamel matrix proteins and proteases: amelogenin, ameloblastin, enamelin, and enamelysin. And later, they contribute to the maturation of the enamel, which is accompanied by a loss of organic matrix and an increase in mineralization (Bailleul-Forestier et al., 2008). The phenotype of AI reflect differences in the timing, during amelogenesis, when the disturbance occurs (Hu et al., 2007).

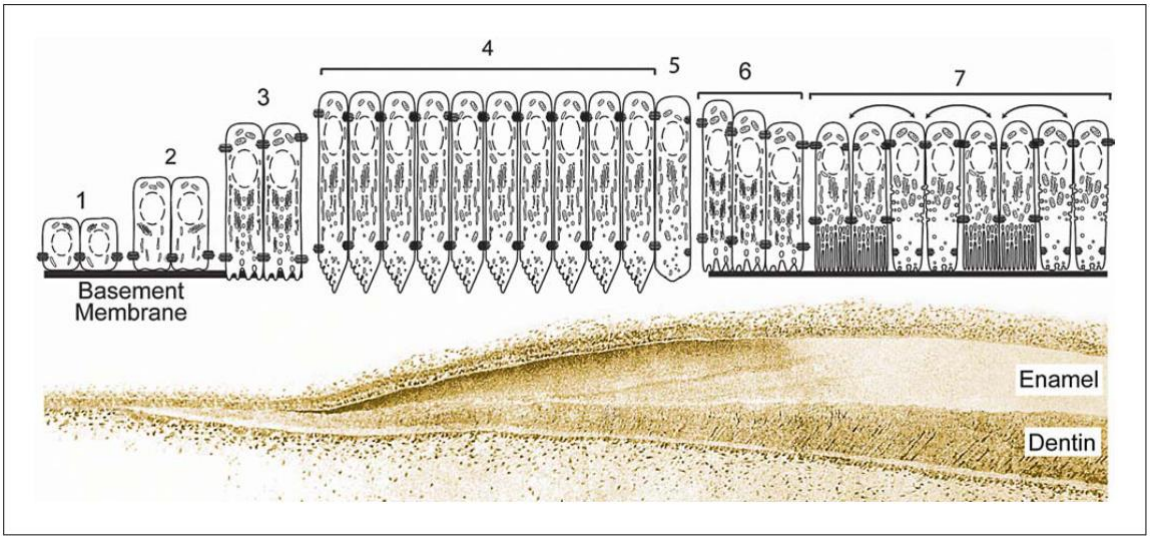


Figure 2. Illustrates the enamel formation process: 1-3 the secretion phase, 4-5 maturation phase and 6-7 mineralization phase (Hu et al., 2007).

Disturbances in formation of the dentin-enamel junction

Sufficient degradation of basal lamina and creation of DEJ in the beginning of enamel formation process point (Fig. 2, stage 1 and 2) is important for normal tooth formation as are the formation of a new basal lamina in the last part of enamel formation (Fig. 2, stage 6 and 7). Odontoblasts initiate the secretion of extracellular matrix that contains mostly type 1 collagen. The collagen molecules extend outward, toward the ameloblasts. An assortment of non-collagenous proteins are also secreted, the most abundant being dentin sialophosphoprotein (DSPP). During the formation of the DEJ, DSPP is secreted by both ameloblasts and odontoblasts (Fukae et al., 2002; Simmer and Hu, 2001).

Degradation of the basal lamina, in the beginning of the process is a main factor to the amelogenesis to occur. Pre-secretory ameloblasts increase in length and penetrating the degenerating basement membrane (Figure 2, stage 3) and initiate the secretion of enamel proteins on the surface of mineralization dentin. This process establishes the DEJ. At the end of the enamel formation process the novel basal lamina containing amelotin (AMTN) (a mammal specific gene) is established at the onset at the maturation stage and continues to exist in the junction epithelium following tooth eruption (Moffatt et al., 2006). If the DEJ is not sufficiently created in the pre-secretory phase the enamel breaks from the dentin as seen in figures 3 and 4 (Fukae et al., 2002; Simmer and Hu, 2001).

Figure 3. AI of hypomineralization form, with breakdown of enamel at DEJ

Figure 4. Radiograph showing breakdown of enamel at the DEJ

The secretory stage

The secretory phase starts with depositing of the aprismatic enamel layer (Fig. 2, stages 1-3). Secretory ameloblasts develop a specialized, cone-shaped Tomes' process at their secretory (distal) ends. The mineralization front retreats with the Tomes process as the enamel crystals

grow in length. Amelogenin, ameloblastin and enamelin are important proteins involved in the secretory phase (Fig. 2, stage 4). Ameloblastin transcribed from the AMBN gene is suggested to have a function in the adhesion of ameloblasts to forming enamel. Enamelin from the ENAM gene is suggested to play a role in lengthening of enamel crystals (Caterina et al., 2002; Hu et al., 2000; Hu et al., 2007; Lindemeyer et al., 2010). In the secretory stage the final thickness of the enamel layer is established. A very thin enamel layer or a layer with pits or groves, with areas of thin enamel, as seen in figures 5 and 6, is a result of disturbances in this phase of enamel formation.

Figures 5 and 6. AI of the hypoplastic form showing both thin enamel (Fig. 5) and the pitted form (Fig. 6).

About 5% of AI cases show an X-linked pattern of inheritance, which are caused by mutations in AMELX. In humans there are two, non-allelic amelogenin genes: AMELX and AMELY. Usually males express a more severe form of AI with brownish severely defected enamel. As having two X-chromosomes girl are usually less affected, but can express wild types. In females with this form of X linked AI there can be lyonization effect (Figs. 7 and 8). Groups of ameloblasts with inactivated mutated amelogenin gene produce normal enamel and groups of ameloblasts with the wild type amelogenin produce defective enamel (Simmer and Hu, 2001; Stephanopoulos et al., 2005; Witkop, 1967). In the dentition this results in a type of mosaicism.

Figures 7 and 8. Girl with X linked form of AI and lyonization. Normal enamel is seen in 46, 45 and 43 while lyonization form of AI is expressed in 16, 15, 14 and 13 with characteristic vertical groves. Typically partial manifestations, only one chromosome is active in the somatic cells of females resulting in a mosaic form.

Maturation stage

During the maturation stage, enamel crystallites grow in width and thickness to replace the lost organic matrix, causing the enamel layer to harden. The ameloblasts move calcium, phosphate, and bicarbonate ions into the matrix and remove water during the maturation phase. During the maturation stage, an evolutionary process occurs in which relatively acid labile mineral is replaced by more acid resistant apatite, the same kind of process that occurs after tooth eruption (Simmer and Hu, 2001).

Figure 9. AI of the hypomaturated form.

Figure 10. AI of the hypomineralized form.

A failure to properly remove the organic matrix and promote the hardening of the enamel layer leads to pathologically soft or hypomatured forms of AI. Kallikrein 4, a protease associated to the gene KLK4 degrades the organic matrix and facilitates the removal of organic matrix from the maturating enamel in the late maturation phase (Hu et al., 2007). Enamelysin has the same effect on tooth maturation but acts in the early maturation phase. The hypomaturation forms display an enamel surface with whitish surface of normal thickness and hardness that can be mistaken for fluorosis (Fig. 9). A failure to properly remove the organic matrix and promote the hardening of the enamel layer leads to a pathologically soft enamel as seen in figure 10. In the hypomineralized form of AI the enamel layer may be of normal thickness, but is rough and soft and wears away quickly following tooth eruption. This is the most severe form of mineralization disturbance (Fig. 10) (Hu et al., 2007).

Genetics of AI

The enamel formation is complicated and involves many genes coding for proteins involved in amelogenesis. A variety of genetic mutations are associated with distinct disturbances in these critical processes that lead to the conditions referred to as AI (Wright et al., 2015). AI may be inherited in an X-linked manner or as an autosomal dominant or recessive trait (Crawford et al., 2007). Autosomal dominant AI typically affects one or more individuals in each generation

of a family. Sporadic cases can be of autosomal recessive origin or due to new mutations or of an autosomal dominant inheritance pattern without penetration of the dominant gene. Some of the genes and possible phenotype expressions are presented in table 1.

Genes coding for AI has been related to other symptoms in the body. An open bite is found in 42% of AI patients and in 24% of their unaffected siblings. Both ENAM and AMELX has been correlated to open bite (Ravassipour et al., 2005). In connection with other syndromes the gene FAM20A seems to have an impact on AI and tooth eruption (Cho et al., 2012). It also influences AI of hypoplastic type with gingival fibromatosis and AI with nephrocalcinosis or enamel-renal syndrome, rare autosomal recessive disorders (Kantaputra et al., 2014; Wang et al., 2014).

The research on genes and proteins coding for AI and other defects associated to thses genes and proteins is rapidly in progress. We mention only a small part of the most important genes and proteins detected to show the complexity of the enamel formation process.

Table 1. Some of the genes involved in enamel formation process and the correlated phenotype.

Genes	**Phenotypes associated with amelogenesis imperfecta**
ENAM	Variable hypoplasia ranging from local pitting to marked, generalized enamel thinning (Wright, 2006) A variety of hypoplastic phenotypes depending on the specific mutation and its effect on the protein (Mardh et al., 2002) Murine ENAM null mouse failed to show any true enamel (Hu et al., 2008)
AMELX	Abnormal maturation and mineralization defects (Wright, 2006) Distinctly abnormal teeth with disorganized, hypoplastic enamel (Gibson et al., 2001) Variable phenotype ranging from hypoplasia to hypomaturation/hypomineralization (Wright et al., 2003)
KLK4 and MMP20	Defects in the final crystallite mineralization or maturation of the enamel (Hart et al., 2004; Kim et al., 2005) The murine Mmp20 null mouse exhibits both hypoplastic and hypomineralized defects (Wright, 2006) Murine Klk4 null mouse exhibits hypomaturation defects (Simmer et al., 2009)
AMTN (Amelotin)	No mutation in the amelotin gene has been related to AI (Santos et al., 2007)
FAM83H	Autosomal dominant hypocalcified AI, normal enamel thickness with decreased mineral content (Kim et al., 2008; Wright et al., 2009)

Dental age and maturity

A significant acceleration of dental age of 1.1±0.8, years similar in both hypoplastic and hypomineralized AI groups, has been reported compared with control children. The population studied had a mean age of 10.4±3.3 years. A sixfold increase in impaction of permanent teeth was found in the same study (Seow, 1995).

Diagnosis of AI

The diagnosis of AI is based on family history, pedigree plotting and clinical observation. Radiographs can show resorption, taurodontism and a poor contrast between dentin and enamel (Crawford et al., 2007). Differential diagnoses, as for example fluorosis, MIH and rickets have to be excluded as well as systemic diseases and syndromes (Crawford et al., 2007). Today it is possible to use genetic tests, to make the diagnosis of AI, but they are expensive and all genes involved have not been identified

Clinical classifications and inheritance pattern

AI is a heterogeneous group of enamel disturbances (Table 2), genomic in origin, which affect the structure and clinical appearance of the enamel of all or nearly all the teeth in a more or less equal manner, and which may be exclusive or associated with morphologic or biochemical changes elsewhere in the body (Aldred and Crawford, 1995; Hu et al., 2007; Witkop, 1988).

Several classification systems for AI have been suggested. The early classifications were made due to the phenotypes – the clinical expression - the most simple classification dividing AI into "hereditary enamel hypoplasia" and "hereditary enamel hypocalcification", (Weinmann et al., 1945). Later on the mode of inheritance was added as a secondary discriminator (Aldred and Crawford, 1995). Evaluation of the phenotype and genotype relationship in AI suggests there are clustering of phenotypes depending on the specific gene involved, the type of mutation and its effect on the translated protein, and the protein functional properties. The demarcation between phenotypes is not always exact with some overlap occurring between hypoplastic and hypomineralization defects (Wright, 2006). For the practitioner these schedules are complex and difficult to use. The mostly frequently used classification is that of Witkop and Rao (1971) and by Witkop (1957) (Poulsen et al., 2008).

Table 2. Some classification systems applied to Amelogenesis imperfecta

Weinmann 1945 (Weinmann et al., 1945)	Two types based only of phenotype: hypoplastic or hypocalcified
Witkop, 1957 (Witkop, 1957)	Classification based primarily on phenotype. 5 types: 1. Hypoplastic 2. Hypocalcification 3. Hypomaturation 4. Pigmented hypomaturation 5. Local hypoplasia Added mode of inheritance as further means of delineating cases.
Witkop and Rao, 1971 (Witkop, 1971)	Classification based on phenotype and mode of inheritance. Three broad categories: hypoplastic, hypocalcified, hypomaturation. a. **Hypoplastic** Autosomal dominant hypoplastic-hypomaturation with taurodontism (subdivided into a and b according to author) Autosomal dominant smooth hypoplastic with eruption defect and resorption of teeth Autosomal dominant rough hypoplastic Autosomal dominant pitted hypoplastic Autosomal dominant local hypoplastic X-linked dominant rough hypoplastic b**. Hypocalcified** Autosomal dominant hypocalcified c. **Hypomaturation** X-linked recessive hypomaturation Autosomal recessive pigmented hypomaturation Autosomal dominant snow-capped teeth White hypomaturation spots?
Witkop and Sauk, 1976 (Witkop CJ, 1976)	Classification based on phenotype and mode of inheritance, similar to classification of Witkop and Rao (1971)
Sundell and Koch, 1985 (Sundell and Koch, 1985)	Classification based solely on phenotype
Aldred and Crawford, 1995 (Aldred and Crawford, 1995)	Classification based on: Molecular defect (when known) Biochemical result (when known) Mode of inheritance Phenotype
Aldred et al., 2003 (Aldred et al., 2003b)	Classification based on: Mode of inheritance Phenotype – clinical and radiographic Molecular defect (when known) Biochemical result (when known)

Impact on having AI

For the patient AI frequently requires lifelong extensive dental treatment. The costs for treatment can be considerably, not only in financial terms but also in time spent during treatment. Most of the studies in AI patients are case reports or cases series and there is a lack

of studies with high impact (Poulsen et al., 2008). The primary clinical problems present in AI patients, regardless of subtype, are unsatisfactory esthetics, dental sensitivity, and loss of occlusal vertical dimension due to the rapid wear (Coffield et al., 2005; Poulsen et al., 2008; Seow, 1993). Adult patients with AI report significantly lower OHRQoL compared to controls (Hashem et al., 2013). Parekh et al. (Parekh et al., 2014) report that children and adolescents with AI have concerns regarding esthetics and function as well as a high level of concern about comments by other people.

Tooth sensitivity

Increased sensitivity in teeth is mentioned as a huge problem in many studies (Aldred and Crawford, 1995; Coffield et al., 2005; Crawford et al., 2007; Lindunger and Smedberg, 2005; Poulsen et al., 2008). In the hypomineralized/hypomatured form of AI the sensitivity problems were found to be more severe than in the hypoplastic form (Seow, 1993). Sensitivity is not usually recorded in the clinic, but when individuals were asked to rate their level of dental sensitivity as normal, mild, moderate or severe, moderate or severe sensitivity problems were found in 46% of the patients (Ravassipour et al., 2005). When eating and drinking as well as when brushing teeth increased sensitivity is a problem. Several studies have highlighted the importance of using efficient local anesthesia, using local anesthesia during scaling and sometimes even general anesthesia (Crawford et al., 2007; McDonald et al., 2012). Use of fluoride can reduce sensitivity problems on some of the AI patients (de Souza et al., 2014). When treating teeth in one jaw or side of the mouth, there could be sensitivity problems in the opposite jaw or side of mouth due to water or air flow (McDonald et al., 2012). Sensitivity problems during dental treatment are common and reported as a risk for dental fear and anxiety when having MIH (Jälevik and Klingberg, 2002). Patients with AI also experience frequent dental treatments in teeth with increased sensitivity as in MIH, both with a risk for developing dental fear and anxiety and behavioral problems.

Enamel breakdown

Enamel breakdown is a problem not only when the DEJ is defective but also in patients with hypoplastic and hypomineralized/hypomaturated forms of AI. The breakdown is usually posteruptive but preeruptive breakdown can be present (Crawford et al., 2007). Extensive wear in the hypomineralized/hypomatured forms of AI or in the form of chipping when eating or biting can occur, resulting in reduction of the vertical dimensions of occlusion (Seow, 1993; Yip and Smales, 2003).

Gingivitis

Enamel is of ectodermal origin as are the gingiva and the skin. A higher prevalence of gingivitis is reported in AI patients (Markovic et al., 2010; Poulsen et al., 2008). Poor oral hygiene is present in some cases but not all. Gingivitis and plaque were more common when having hypomineralized form of AI (Lindunger and Smedberg, 2005). Gingivial hyperplasia (enlargement of the gingival tissue) has been found to be associated with FAM20A and associated to enamel defects in AI (Cherkaoui Jaouad et al., 2015; O'Sullivan et al., 2011). High levels of calculus and periodontial disease is reported in adult paitients with hypomineralised AI, but only in case reports (Sundell, 1986).

Bonding strength

The bonding strength to enamel is lower in hypomineralized/hypomatured AI and may be correlated to specific gene defects (Simmer and Hu, 2001). Hypocalcified enamel have a higer content of protein by weight (3-4 %) compared to normal enamel (0.5 %) resulting in a lower bonding strength (Saroglu et al., 2006). Analysis of bonding strength in primary teeth with hypocalcified AI compared to healthy primary teeth showed significantly lower bonding strength in AI affected teeth (Saroglu et al., 2006). Hardness of normal permanent tooth enamel was significantly higher than hardness of enamel affected by AI in permanent teeth (Faria-e-Silva et al., 2011). The bonding strength was 14.2±4.8 MPa compared to 24.0±7.6 MPa in healthy teeth. Even dentin was affected and showed a lower bonding strength but not lower hardness. Lower mineral content in the enamel is supposed to cause the decrease of bond strength (Faria-e-Silva et al., 2011). Below hypocalcified enamel, resides a layer of sclerotic dentin. One hypothesis for the existence of this layer is that continuous irritation stimulates the odontoblasts, causing dentin sclerosis (Saroglu et al., 2006). This defective bonding results in a poor clinical performance of of resin composite restorations and many replacements particularly in childhood and adolescence (Crawford et al., 2007; McDonald et al., 2012).

New crown materials

In recent years, the development of all-ceramic restorations has made it possible to make crown restorations with quality and longevity comparable to metal-ceramic crowns (Esquivel-Upshaw et al., 2013; Pelaez et al., 2012). Recently, high-termed pressed lithium disilicate glass crowns (IPS e.max Press) showed similar clinical outcomes to presintered zirconium dioxide covered by porcelain (Procera AllCeram) and metal ceramic crowns (Etman and Woolford, 2010). Procera and IPS e.max Press have different properties. In Procera, the tendency for chipping is higher, transparency lower, and the need for thickness

of material higher, as more tooth material needs to be removed (Al-Amleh et al., 2010; Al-Amleh et al., 2014). Yet, IPS e.max Press has a transparency that can give color problems when restoring dark or yellow teeth and is less tested in long-term studies (Etman and Woolford, 2010).

Guidelines and tretment recommendations

Current guidelines for treatment of patients with AI recommend to cover anterior teeth if necessary with composite resin or glass ionomer with replacements anticipated, and molars with steel or gold crowns (Crawford et al., 2007; Markovic et al., 2010; McDonald et al., 2012; Seow, 1993). Prosthetic crown therapy should be postponed to adulthood. Some authors suggest composite crowns during childhood and adolescence (de Souza et al., 2014; Millet and Duprez, 2013). Treatment plan is related to the age of the patient, the type and severity of the disorder and the oral health of the patient. All authors recommend optimizing the oral hygien during childhood and adolescents. Some authors mention patients suffer from esthetical problems and a wish for permanent therapy in an earlier stage (Crawford et al., 2007; Lindunger and Smedberg, 2005). There is a lack of evidence based studies on treatment of young patients with AI (Dashash et al., 2013).

Longevity of restorations

There are case reports or case series reporting therapy of young AI patients (Ayers et al., 2004; Dashash et al., 2013; Gokce et al., 2007; Markovic et al., 2010; McDonald et al., 2012; Ozturk et al., 2004; Suchancova et al., 2014; Urzua et al., 2011; Yip and Smales, 2003). Many authors report that replacements of resin composite restorations are common and to be anticipated (Crawford et al., 2007; Markovic et al., 2010; Urzua et al., 2011).

Esthetical problems

Esthetical problems are common and the cause of lower self-esteem, social avoidance and a reduced quality of life (Aldred et al., 2003a; Coffield et al., 2005; Parekh et al., 2014). Therapy to solve esthetical problems range from bleaching to full coverage prosthetic therapy, depending of severity and expression of AI.

Orthodontic aspects

Bonding of fixed appliances is a problem when treating AI patients. Not only loss of brackets, rebonding of brackets and prolonged treatment periods but also the risk of fractures when rebonding is a challenge to the orthodontist (Arkutu et al., 2012). Traditional banded

appliances, use of plastic brackets or the use of glass ionomer could be a possibility overcoming some of these problems. If no measures are taken to protect tooth wear, a decrease in vertical height could also be a problem. Other problems could be delayed tooth eruption, impacted teeth, retention of teeth, congenitally missing teeth and root malformations (Arkutu et al., 2012). Taurodontism and pulpal callcifications have also reported as risk factors.


Figures 11 and 12. Patient with hypoplastic form of AI 18 years old at start of crown therapy (Fig. 11), and 3 years after crown therapy showing spontaneous correction of anterior open bite (Fig. 12).


Figures 13 and 14. Patient with hypomineralized form of AI at 9 years of age at start of crown therapy (Fig. 13). Two years after anterior crown therapy (Fig. 14).


Figures 15 and 16. Showing visible crown margins at 19 years of age with enamel breakdown at margins (Fig. 15). Crowns 13-23 were remade at 20 years of age (Fig. 16).

Open bite is a common problem among AI patient (Rowley et al., 1982; Sundell, 1986). In the hypocalcified typ of AI, open bite were present in 43% of the AI affected patients (compared to 3-7% in the general population), 35% of skeletal origin and in 14% of the unaffected family members. Unaffected family members had a markedly higher prevalence (12%) of dental and/or skeletal open bite compared to general population (Ravassipour et al., 2005). Mutations

in both ENAM and AMELX genes are described to be associated to open bite (Ravassipour et al., 2005). Patients with long face syndrome, have a risk for visible margins when compensation for open bite occurs (Figs. 11-16).

Clinical problems

When treating a growing person with a developing occlusion considerations must be taken to both physical and psychological maturity. An early therapy plan and to ensure an initial positive experience of dental treatment is essential. Expectations from children, adolescents and parents has to be met and taken in account. Taking care of pain and use local anesthesia as well as analgetics and sedation if nessessary is important not to contribute to development of dental fear and anxiety. Arrangement has to be made not to interfer too much with parents work situation and the young patients school situation (McDonald et al., 2012). Patients requiring extensive dental treatment also have and increased risk for dental fear and anxiety, uncooperative behavior and to discontinue therapy.

Oral health related quality of life

Patient reported outcomes (PROMs) can be defined as: "reports coming directly from patients about how they feel or function in relation to a health condition and its therapy without interpretation by healthcare professionals or anyone else". The use of PROMs has come from the shift from a biomedical perspective to a broader bio-psychosocial model of health (Engel, 1977). The most obvious advantages of this are that patients themselves are in the best position to assess the improvement in their symptoms or quality of life. As many dental conditions have psychological and social implications; PROMs should supplement dental outcome measures (Cushing et al., 1986). Following the development of measures for use in adults, several questionnaires have been produced for use with children or using parents as proxies. Among them are the child perceptions questionnaire (CPQ) (Jokovic et al., 2002), the child oral impacts on daily performances index (C-OIDP) (Gherunpong et al., 2004), the Child Oral Health Impact Profile (COHIP) (Broder and Wilson-Genderson, 2007). The age ranges for these instruments are from 8-15. Therefore not ideal for our purposes since the majority are adolescents and young adults.

Oral health impact profile

The oral health impact profile (OHIP) is an instrument that measures individuals perception of the social impact of oral disorders on their well-being. The 49 questions in the OHIP capture seven conceptually formulated dimensions: functional limitation, physical pain,

psychological discomfort, physical disability, psychological disability, social disability and handicap. The development, reliability and validity of the OHIP have been described previously (Slade and Spencer, 1994). Particularly in health outcomes research the use of several instruments are required. Each instrument needs to be as short as possible yet having the same characteristics as the original instrument. Therefore OHIP-14 was designed and found to have good reliability, validity and precision (Slade, 1997). It is important in clinical studies of treatment effects that the chosen instruments have longitudinal validity, reproducibility and the ability to detect minimally important clinical changes. Locker (2004) found that the OHIP-14 had excellent test-retest reliability, the minimally important difference was 5 points on a Likert scale and that it was responsive to change. It cannot be assumed that instruments that are designed for adults are appropriate for children and adolescents (Locker et al., 2004). OHIP-14 has been used in a study of 15-17 year-olds with regard to level of oral health measured both by oral health indicators and clinical examination. OHIP-14 was found to be a valid and reliable instrument measuring their OHRQoL (Ravaghi et al., 2011). OHIP-14 has been questioned in Sweden because the low caries prevalence can make it difficult to assess differences in OHRQoL particularly in studies on caries prevention (Oscarson et al., 2007). Recently evidence has emerged for a four-dimensional structure of the OHIP-14 (John et al., 2014). The four identified factors were named oral function, orofacial pain, orofacial appearance, and psychosocial impact.

Thematic analysis

Thematic analysis (TA) can be seen as a basic method for qualitative analysis (Braun and Clarke, 2006). Identifying "thematizing meanings" is one of a few shared generic skills across qualitative analysis (Holloway and Todres, 2003). Thematic analysis is considered to be independent of theory (such as grounded theory), and can be applied across a range of theoretical approaches (Aronson, 1994; Roulston, 2001), Thematic analysis is a method for identifying, analyzing and reporting patterns (themes) within data. The data can be interviews, written material such as articles or transcripts from TV programs. TA organizes and describes the data set in detail. However, frequently if goes further than this, and interprets various aspects of the research topic and tries to analyze the meaning of the data obtained (Boyatzis, 1998).

AIMS OF THE THESIS

General aim

The general aim of this thesis was to investigate the quality and longevity of therapy recommended today for dental treatment of patients with AI and how oral health related quality of life is affected. The aim was also to study the outcome of early crown therapy, possible adverse outcomes and how this treatment affects quality of life outcomes. Furthermore to investigate adolescents and young adults' experiences of living with AI and receiving early crown therapy.

Specific aims

Study I

The aim of was to investigate dental health, number of dental visits and reason for the visits, quality and longevity of restorations in patients 6-25 years old with AI compared to a control group. A secondary aim was to study differences regarding longevity of restorations between patients with hypomineralized/hypomatured AI and hypoplastic AI.

Study II

The aim was to compare the quality and longevity of two crown types Procera and IPS e.max Press in adolescents and young adults with AI in a randomized controlled trial. A secondary aim was to document adverse events.

Study III

The aim was to investigate oral health related quality of life, dental fear and anxiety, as well as attitudes towards dentistry in a group of adolescents and young adults with AI. A secondary aim was to investigate the same variables after early crown therapy.

Study IV

The aim was to explore experiences and perceptions of living with AI and having early prosthetic therapy among adolescents and young adults.

MATERIALS AND METHODS

Patients

Study I

The study population comprised 82 patients with AI who had been referred from 22 Public Dental Service (PDS) clinics in the county of Dalarna to the specialist pediatric dentistry clinic in Falun (Fig. 18). The patients included came from rural areas and small towns. Inclusion criteria were age (6 to 25 years) a clinically verified AI diagnosis, confirmed by anamnestic familiar history or histological examination. Exclusion criteria were patients with fluorosis, MIH other oral developmental disturbances, systemic disorders, or patients who were unable to provide informed consent. Patients were grouped into those with hypoplastic AI and those with hypomineralized/hypomatured AI. For comparison, we selected a matching control group from the PDS (one control per AI case), matched by age, gender, and residential area. Patients enrolled in the study from December 2008 to February 2013.

Study II

The study population comprised 27 patients suffering from severe AI, all were in need and asked for prosthetic therapy. They were all collected from the sample of 82 patients in study I (Fig. 18). All patients offered prosthetic therapy agreed to participate in the study. Patients were grouped into those with hypoplastic AI and those with hypomineralized/hypomatured AI. Patients were enrolled in the study from May 2009 to March 2012

Study III

The study population comprised the same patients as in study I (Fig. 17). The same control group was used but two control groups were added, one with MIH and one group with CLP. All controls were matched for age and gender. Patients enrolled in the study from December 2008 to February 2013. The MIH patients were identified from PDS records with the diagnostic code MIH. This group was selected as they exhibit similar problems as patients with AI do, including increased sensitivity, frequent dental treatments, and a higher level of dental fear and anxiety (Jälevik and Klingberg, 2002). The definition of MIH used in this study was: hypomineralization of systemic origin of one to four first permanent molars that is frequently associated with affected incisors (Weerheijm et al., 2001). Patients with CLP were enrolled from the Stockholm Craniofacial Center. The patients with CLP were included as they exhibit disturbances in dental development, frequent dental treatments, esthetic challenges, and

persisting sequelae after completion of therapy. They also report a lower OHRQoL (Antonarakis et al., 2013; Wehby and Cassell, 2010).

Study IV

The fourth study included seven patients receiving crown therapy in study III (Fig. 17). Patients living nearby the cities Falun and Borlänge were asked to participate in a face-to-face interview. The interviews were performed during March 2015.

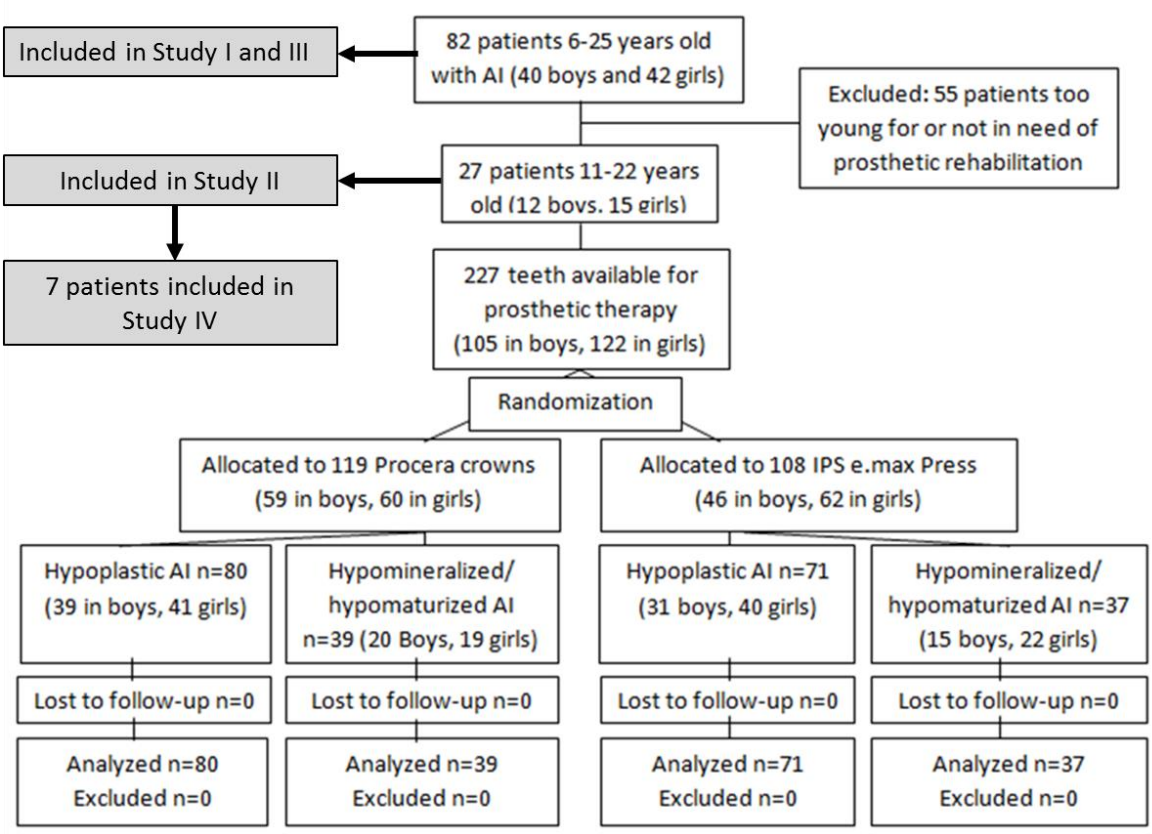


Figure 17. Flow chart of patients included in studies I-IV.

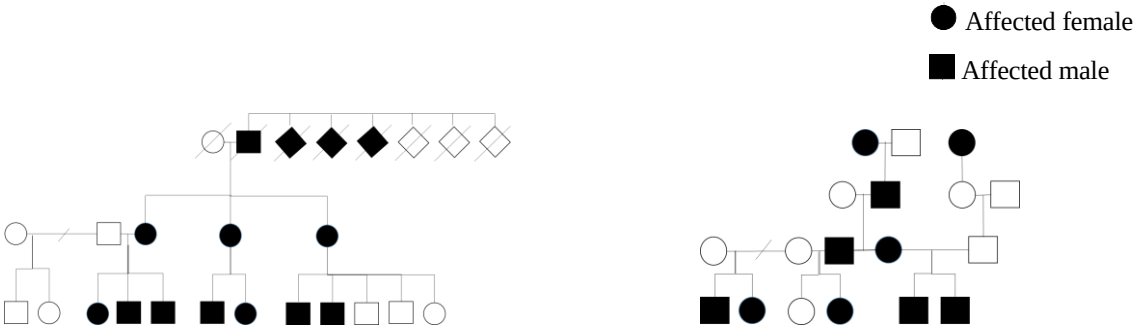
Information and agreement

In all studies patients received written information and gave informed consent to participate. If younger than 18 years of age both parents and the young patient gave their informed consent. After permission, documented in dental records, from parents and patient some data was collected retrospectively from dental records in study I.

Materials

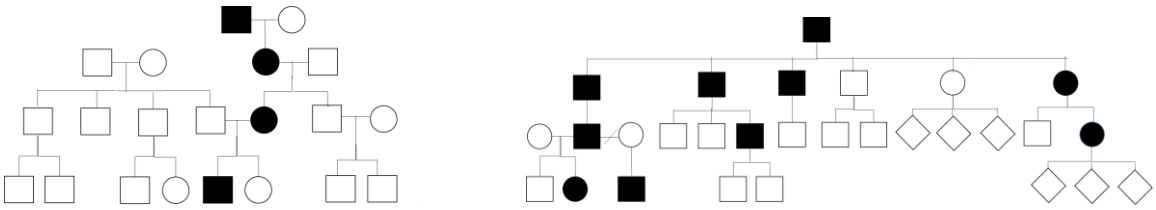
Clinical and radiographic examinations (I, II)

For the AI patients the clinical examination was performed at the Department of Pediatric Dentistry, Falun and for the controls by GPL at their PDS clinic. The examination included a family history, excluding possible differential diagnoses and diseases during childhood for the AI patients (Gadhia et al., 2012). GPL examined all patients, but an independent examiner performed the clinical examination when restorations were made by GPL. Pedigrees were plotted in patients with a family history of AI. Examples of the pedigrees are shown in Figures 18 a-d.



Figue 18 a.Patients from three familes with hypomineralized form of AI

18 b Family with hypoplastic form of AI



18 c. Family with hypoplastic form of AI

18 d. Family with hypomineralized type of AI

The severity of AI was recorded in each tooth as mild, moderate or severe, as modified from Jälevik et al., (2001). In mild cases less than 1/3 of the tooth surfaces were affected by changes in enamel mineralization and the teeth had normal sensitivity. In moderate cases 1/3 to 2/3 of the tooth surfaces were affected by changes in enamel mineralization and the teeth had moderate sensitivity (can perform activities of daily living) and in severe cases more than 2/3 of the tooth surfaces were affected and the teeth exhibited a high sensitivity (Jälevik et al., 2001).

Dental caries (I, II)

Dental caries was diagnosed during the clinical examination, which also included bite-wing radiographs if the available radiographs were more than 2 years old. Manifest caries was diagnosed as grade 3-5 (Amarante et al., 1998).

Gingivitis and periodontitis (I, II)

Gingival bleeding was recorded by pressing a blunt probe without pain onto the orifice of the gingival crevice on mesial and distal surfaces, percent of bleeding sites was presented (Ainamo and Bay, 1975). Periodontal disease was diagnosed as described by Nyman and Lindhe (2003) (Nyman and Linde, 2003).

Apical status (I, II)

Endodontic diagnoses was recorded (Orstavik et al., 1986). Apical radiographs were collected if not available in cases of traumatic history. In study III apical radiographs were taken one and two years after last cementation of crown.

Quality of restorations (I, II)

Number of restorations, type of restoration and quality of restoration were recorded. Quality of restorations was recorded comparing anatomic form, marginal integrity, surface and color according to California Dental Association (CDA), 1977 (Quality Evaluation for DentalCare. Guidelines for the Assessment of Clinical quality and Proffessional Performance., 1977; Ryge and Snyder, 1973; Ryge and DeVincenzi, 1983). Final evaluation of each crown was determined by the lowest value chosen for the three clinical characteristics evaluated.

Table 3. Evaluation of restorations was made according to the quality criteria of the California Dental Association (CDA). Anatomic form, marginal integrity, surface and color are evaluated. (Ryge and DeVincenzi, 1983)

	Rating	Operational Explanation
Acceptable Quality	Excellent	The restoration is of acceptable quality and is expected to protect the surrounding tissue
	Acceptable	The restoration is of acceptable quality but exhibits one or more features which deviate from the ideal
Not Acceptable Quality	Replace or Correct for Prevention	Future damage to the tooth and/or the surrounding tissue is likely to occur
	Replace Statim	Damage to the tooth and/or the surrounding tissue is now occurring

Tooth sensitivity (I, II)

Patients recorded tooth sensitivity on a visual analogue scale (VAS). The examiner recorded the score in millimeters using the same ruler during the study, a score below 3 was considered to indicate no or low pain (Breivik et al., 2008).

Information from dental records (I)

Information from data records included number of dental visits, cause for the visits, time for restoration, time for and cause of replacements and material used.

Registration and randomization (II)

Study II was registered at http://www.controlled-trials.com (ISRCTN704386 27). We used a randomized split-mouth design and a patient-blind data acquisition protocol. We used the number generator table from http://random.org for the randomization process, selecting the first crown material in the side section of the jaw by the upcoming number in the table, which stipulated the type of material for the whole section. We then used the other material on the opposite side of the jaw, creating a "split-mouth method." In the front sections (13-23 and 33-43), the randomization process decided the material to be used for the entire front section and for each jaw separately. The type of crown was blinded to the patient and to the external examiner during the first control examination. Thereafter, radiographs taken during the 1- and 2-year controls made it impossible to blind crown type to the examiner.

Treatment protocol (II)

A standardized schedule were set and followed in treatment procedure on all patients: The patients were given paracetamol one hour before treatment and ibuprofen in combination with paracetamol throughout the rest of the day. Sedation with nitrous oxygen was offered to all patients, and 18 accepted. Local anesthesia was given using Xylocaine dental (20 mg/ml lidocaine hydrochloride + 12.5µg/ml adrenalin). We also covered not anesthetized teeth with fluoride varnish during crown preparation.

The patient and dental technician selected the color and shape of the crown using a specially adjusted light. If there were any difficulties in the shape or position of crowns, mock-ups were made on casts. A pre-prosthetic impression to produce temporary crowns was made using Luxatemp (DMG) or Unifast LC (GC) temporary material, set with Temp-Bond temporary cement (Kerr). Two types of burs were used, both with a rounded top: Parmax 12 212A and Parmax 9 209A (from Parmax AB). For tooth preparation, a high-speed turbine was used; as

little tooth substance as possible was removed, without reducing the recommended thickness of the porcelain. Two strings of Ultrapac 0 retraction cord (Ultradent) with Viscostat Clear and 25% aluminum chloride (Ultradent) for hemostatic effect were used, leaving one string while the impression material set. Permadyne Penta H, polyether impression material (3M ESPE) was mixed in Pentamix 3 (3M ESPE) in a Triple Tray. An elastomer syringe spread the Permadyne Garant 2:1 light body (3M ESPE). Exactly 6 minutes setting time was allowed.

The same pediatric dentist (GPL) placed all the restorations. With the exception of one crown, made in the same laboratory, the same two dental technicians made all the crowns. The crowns were made either of zirconia dioxide coping with Vita porcelain (Procera, Nobel Biocare) or lithium disilicate glass-ceramic (IPS e.max Press, Ivoclar Vivadent). Crowns were cemented after 8 to 21 days using local anesthesia, analgesics, and nitrous oxygen. One string of Ultrapac 0 retraction cord with Viscostat Clear was inserted into the gingival pocket, where it remained during cementation. After brushing with a pumice-stone in a rubber-cup, technicians cleaned the surface with Ultra-Etch 35% phosphoric acid (Ultradent). Crowns were also cleaned with Ultra-Etch 35% phosphoric acid (Ultradent). Bonding agent Scotchbond 1 XT (3M ESPE) was used on the tooth. Rely X ARC cement was spread inside the crown after application of the primer for Rely X ARC cement, and the crown was gently pressed onto the tooth; excess cement was removed with a Quick Stick. After light curing the cervical parts of the crown for 20 seconds each, buccal and lingual, the strings and cement were removed using a curette. The treatment protocol included cleaning the crowns with Ultra-Etch 35% phosphoric acid before cementation. This is usually not recommended, but no loss of crowns occurred.

Questionnaires (III)

In study II all AI patients and the healthy controls from PDS clinics were asked to answer three questionnaires directly after an oral examination. We sent questionnaires to patients in the MIH and CLP groups by land mail in November 2012 and included a self-addressed, stamped envelope. These groups received one reminder four months later.

OHIP-14 (III)

For estimation of oral health related quality of life (OHRQoL) we used the 14-item oral health impact profile (OHIP-14) (Slade, 1997), a short version of the OHIP-49 (Slade and Spencer, 1994). The OHIP-14 is preferable when studying OHRQoL on a population basis and attempting to detect changes over time (Locker and Allen, 2002). The OHIP-14 scale uses a five-point Likert-scale (never=0, seldom=1, sometimes=2, fairly often=3, and very often=4)

for responses. The Swedish version has been tested for reliability and validity (Larsson et al., 2004). We used the four dimensions of impact: orofacial pain, oral function, orofacial appearance, and psychosocial impact (John et al., 2014). We excluded subjects with more than five missing OHIP-14 responses, if there were five or fewer missing responses, the missing values received the subject's median response score (John et al., 2014).

CFSS-DS (III)

To estimate dental fear and anxiety we used the children's fear survey schedule – dental subscale (CFSS-DS) (Cuthbert and Melamed, 1982). This psychometric scale consists of 15 items, where each item can give a score from 1 (not afraid) to 5 (very afraid). Thus, possible total scores range from 15 to 75. Calculations suggest a population-based mean value on the CFSS-DS of 23 (SD 8) for 9–11-year-old Swedish children (Klingberg et al., 1994). A score ≥38 indicates dental fear (Klingberg, 1994). For the CFSS-DS questionnaires with fewer than five items missing, we replaced missing items using specific-item means (ten Berge et al., 2002).

DBS-R (III)

To explore the interpersonal processes and relationships between the patient and the dental care provider we used the dental belief survey, revised version (DBS-R) (Kvale et al., 2004). It includes 28 items, covering three dimensions of the interpersonal relationship as conceived by the patient: the ethical dimension, communication, and control. Each item has five score levels from 1 to 5 with 1 indicating no concern and 5 indicating greatest concern. The outcome of the DBS-R is a sum of scores ranging between 28 (highly positive) and 140 (highly negative) (Abrahamsson et al., 2009). A total score >42 is the cut-off indicating negative attitudes towards dental care (Abrahamsson et al., 2006). Patients were excluded if more than 20% of their items contained missing data (Kvale et al., 2004).

The process of thematic analysis (IV)

In-depth interviewing is a qualitative research technique that involves conducting intensive individual interviews with a small number of respondents to explore their perspectives on a particular item. We used in-depth interviews to get detailed information about the young patients thoughts and behaviors and to get more in depth knowledge about how life is living with AI (Boyce and Neale, 2006). The topic of discussion was the young person's experiences of living with AI and the dental treatment provided. The principal investigator

(GPL) performed crown therapy for all patients and an independent psychologist (TH), experienced in cognitive behavior therapy for dental phobia in children and adolescents, made all interviews. She let the patient take the lead and only asked follow-up questions when necessary or when discussion faded out. An independent colleague experienced in qualitative research transcribed the interviews verbatim. The transcripts were controlled and compared to the recorded data by TH, GPL and the co-supervisor. All patients were given pseudonyms in the text. We analyzed the transcripts from the interviews using thematic analysis according the method of Braun and Clarke (Braun and Clarke, 2006). Thematic analysis can use a 'realist' approach, reporting experiences and meaning, or a 'constructionist' approach, reporting the different discourses operating in the setting. This study used a 'contextualist' method, in between realism and constructionism, to interpret how participants make meaning and how the social context influences these meanings. First we familiarized ourselves with the data by listening to the recorded verbatim and read and re-read the transcribed interviews several times. We coded all interviews for interesting features, and made thematic maps on features related to the research questions. After sorting data we searched for potential themes and created a mind-map with possible themes for the whole data. To identify a theme, it must satisfactory answer the question "what is this expression an example of?" (Braun and Clarke, 2006). When a set of candidate themes was identified we revised the themes and considered the validity of individual themes in relation to the data set. Then we defined and re-defined the themes, and analyzed the data within them. Finally we were able to write the report.

Statistical analyses

Study I

The Mann-Whitney U-test was used in the cross-sectional study for comparisons between the two groups and the Pearson correlations test for bivariate correlations. The chi-square trend test compared the quality of restorations between groups. We plotted Kaplan-Meier survival curves for patients with AI, subgroups of AI, and control patients, compared survival curves within groups using the log-rank test, and used right censoring to analyzse the survival of restorations. Multilevel Cox regression analyses helped identify factors related to the survival of restorations.

Study II

The chi-square trend test and Fisher exact test compared the quality of restorations among groups. We drew Kaplan-Meier survival curves for patients with AI, subgroups of AI, and type of crown material, comparing survival curves within groups using the log-rank test and right censoring to analyze the survival of restorations. Independent-sample *t* test and Wilcoxon signed-rank test were used to compare different outcome of gingivitis and VAS score. Multilevel Cox regression analyses helped identify factors related to the survival of restorations. Spearman rank correlation was used to test bivariate correlations to change in VAS score. A *p*-value <0.05 was considered as statistically significant.

Study III

The Mann-Whitney U-test examined differences between groups. Logistic regression analyses evaluated the influence of age, gender, visits per year, severity of AI, and VAS score on the dependent variables of OHRQoL, dental fear, and dental beliefs. Cronbach's alpha calculated the internal consistency reliability of the OHIP-14 scale. Treatment effects of crown therapy in patients with severe AI were compared with the Wilcoxon signed rank test, and ES calculated with Cohen's *d* based on pooled standard deviations. We considered a treatment effect to be trivial if ES was <0.20, small if $0.2 \leq ES < 0.5$, moderate if $0.5 \leq ES < 0.8$, and large if $0.8 \leq ES$.

All analyses were done using the Statistical Package for the Social Sciences (SPSS, versions 20- 22; Chicago, IL, USA).

RESULTS

Dental caries and gingivitis (I)

We found significantly higher levels of dental caries and gingivitis in patients with AI compared to controls. DMFS was 8.1±15.6 in the AI group compared to 1.0±2.0 in the control group ($p<0.001$). When only restorations due to dental caries were included, DMFS was 2.5±4.1 in the AI group and 0.8±1.8 in the control group ($p<0.001$). Mean of GBI% in the AI group was 26.9 ± 24.6 and 12.8 ± 14.8 in the control group ($p<0.001$).

Quality of restorations (I)

The retrospective study of dental records found 326 composite resin restorations among AI patients and 63 composite resin restorations in the control group. The analysis of restoration quality in the AI group showed that 14% were diagnosed as excellent, 43% as acceptable, 33% in need of replacement and 10% as immediate danger for the tooth. The corresponding values in the control group were 51%, 36%, 11%, and 2% ($p<0.001$) (Fig. 19). Restorations in the AI sample also included 120 Procera porcelain crowns (zirconia dioxide coping with Vita porcelain); 132 IPS e.max Press (lithium disilicate glass-ceramic) porcelain crowns; and 45 Empress (leucite-reinforced ceramic) veneers, partial coverage restorations, and crowns.

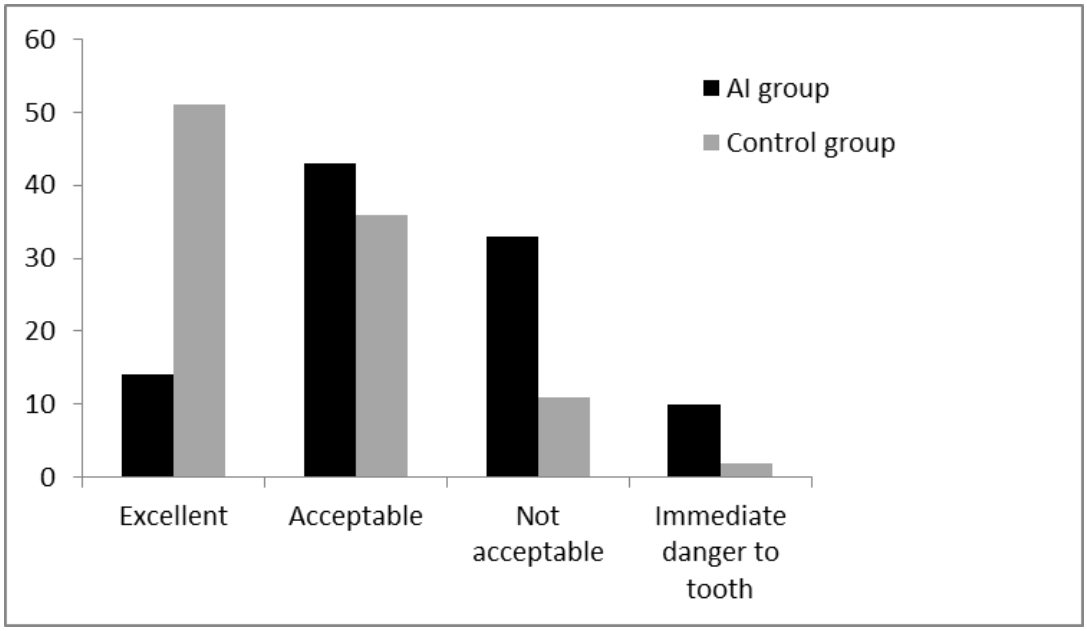


Figure 19. Quality of restorations (%) separately in AI group and control group ($p<0.001$). Quality criteria of the California Dental Association were used (see table 3).

Replacement of restorations and dental visits (I)

We found that 9.5±15.7% of the AI group's visits to the dental clinic was to replace restorations, compared to 1.9±5.0% in the control group (p<0.001). During the observation period 24.7±35.1% of restorations in the permanent and deciduous teeth of patients with AI failed, compared to 9.2±23.7% in the control group (p<0.001). As a consequence of this, the total number of visits per year in the AI group, 2.9±1.7, was significantly higher than the control groups 1.9±1.3 (p<0.001). The reasons for restoration failures in the AI group included loss or fracture of restoration and/or tooth (63%), recurrent caries (14%), tooth sensitivity problems (12%), trauma (5%), esthetic problems (3%), deficit of restoration material (2%), and endodontic problems (1%). Restoration failures in the control group were due mainly to recurrent caries (35%), loss or fracture of restoration and/or tooth (27%), trauma (17%), and endodontic problems (17%) (p<0.001).

The total number of visits per year in the AI group, 2.9±1.7, was significantly higher than the control group 1.9±1.3 (p<0.001). As shown in figure 20, the number of dental visits per year in the AI group increased with age while they decreased in the control group

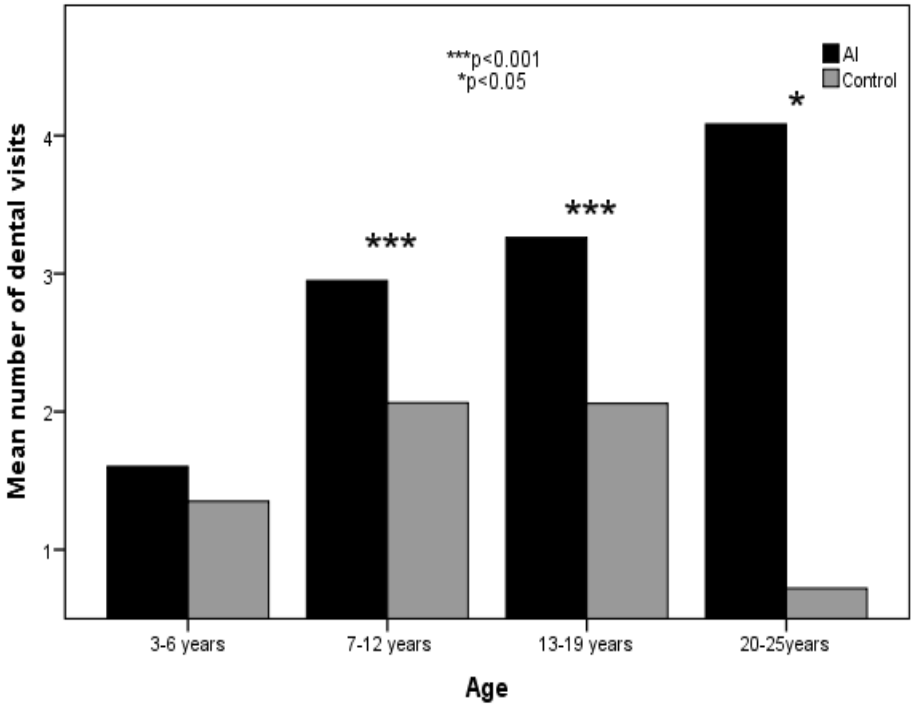


Figure 20. Mean number of dental visits in different age groups.

Sensitivity (I)

Tooth sensitivity scores measured on a VAS were significantly higher in the AI group, 4.0±2.6, than in the control group, 1.3±1.5 ($p<0.001$). When both groups were analyzed together, VAS scores correlated significantly with the number of replaced restorations ($r=0.232$; $p=0.002$).

Survival of restorations (I)

The longevity of composite resin restorations was significantly lower in the AI group than in the control group (Fig. 21). In the AI group, the 5-year survival rate was 50%, compared to 80% in the control group ($p=0.008$). However, we found no significant difference between the AI and control groups in the longevity of glass ionomer restorations ($p=0.564$).

Regarding the different forms of AI we found that the longevity of composite resin restorations (Fig. 22) was significantly longer for patients with hypoplastic AI (58%) than for patients with hypomineralized/hypomaturated AI (47%) ($p<0.01$).

Survival of composite resin restorations had decreased longevity in patients diagnosed with moderate and severe forms of AI (Fig. 23).

Longevity of Procera, IPS e.max Press and Empress were significantly higher compared to longevity of composite resin restorations in AI group (Fig. 24) ($p<0.001$). Of these various restoration methods, 94% of Procera crowns, 99% of IPS e-max-Press crowns, and 75% of Empress veneers, partial coverage restorations, and full crowns were of excellent or acceptable quality.

Quality of crown therapy (II)

After randomization, 227 crowns were made, these included 119 Procera crowns and 108 IPS e.max Press crowns: 80 Procera in the hypoplastic AI group, with 39 in the hypomineralized/hypomatured AI group, and 71 IPS e.max Press in the hypoplastic AI group, with 37 in the hypomineralized/hypomatured AI group (Fig. 17). Mean age at crown therapy was 17.9±3.4 years.

When comparing the Procera and IPS e.max Press groups, we found no differences with regard to age at crown therapy, type of AI, sex, traumatic history, or apical status. After 2 years, 97% of the crowns in both crown groups were in excellent or acceptable condition.

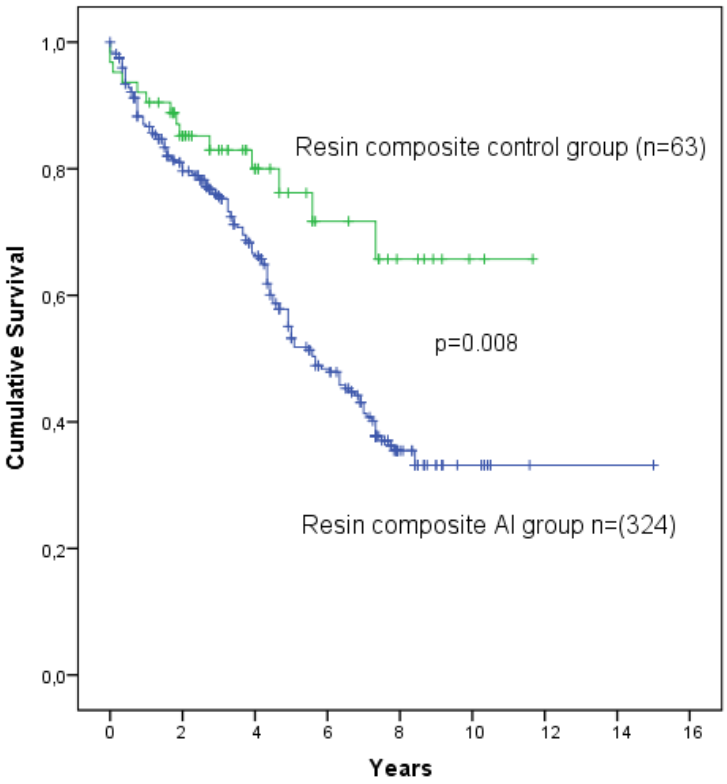


Figure 21. Longevity (years) of composite resin restorations in AI and control groups. Log-rank test.

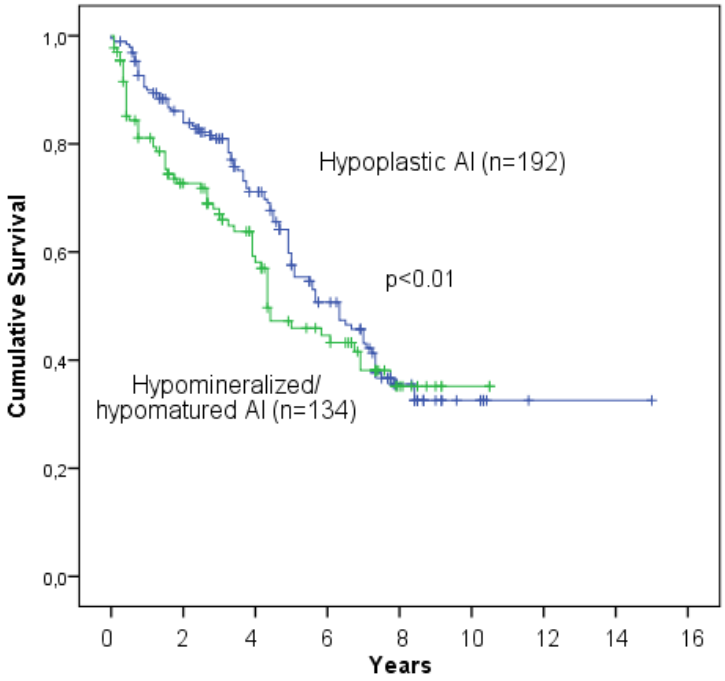


Figure 22. Longevity (years) of composite resin restorations in hypoplastic and hypomineralized/hypomatured forms of AI. Log rank test

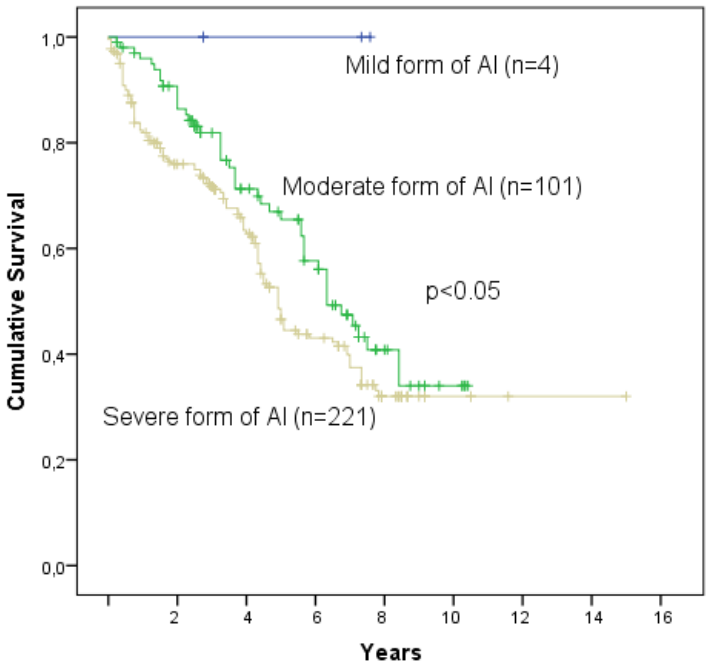


Figure 23. Longevity (years) of composite resin restorations in relation to severity of AI between severe and moderate forms. Log rank test.

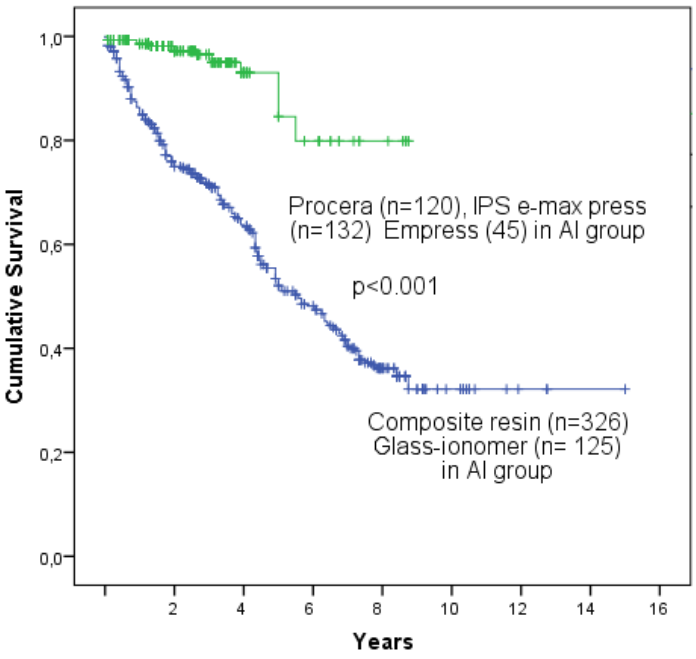


Figure 24. Longevity (years) of Procera, IPS e-max press and Empress prosthetic restorations compared to composite resin and glass-ionomer restorations in patients with AI. Log rank test.

Longevity of restorations (II)

A Kaplan-Meier plot shows no significant differences in longevity of Procera and IPS e.max Press crowns in AI patients (Fig. 25). The tooth had to be fully erupted before the start of crown therapy. This made it impossible to make all crowns in the dentition at the same time during adolescence. Because of this, the final observation period ranged between 24 and 60 months.

Sensitivity before and after crown therapy (II)

Figure 26 shows that 24 of 27 patients had a reduction in sensitivity 2 years after crown therapy. Three patients (1 with pulpitis, 1 with apical periodontitis, and 1 without endodontic complications) showed increased sensitivity after porcelain crown therapy. The median VAS score was reduced from 5.2 (0 to 8.4) to 0.6 after 2 years (0 to 5.5) ($p<0.001$).

Adverse events (II)

Seven patients experienced adverse events in 12 teeth. The adverse events involved development of apical periodontitis (3% of crowns), and all cases but 1 were related to the experience of dental trauma. Difficulties with impressions or cementation had resulted in suboptimal design of crowns or shortage of cement. In 1 case, chipping was diagnosed, also related to dental trauma.

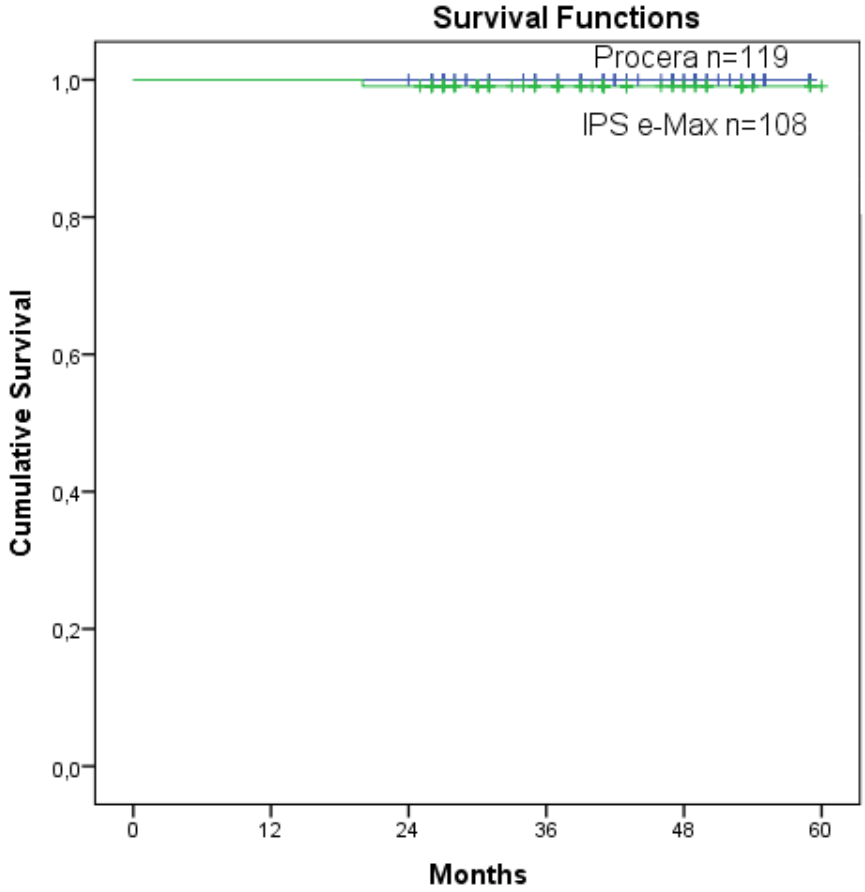


Figure 25 Longevity (in months) of Procera and IPS e.max Press crowns (cemented in patients between 11 and 22 years) with AI.

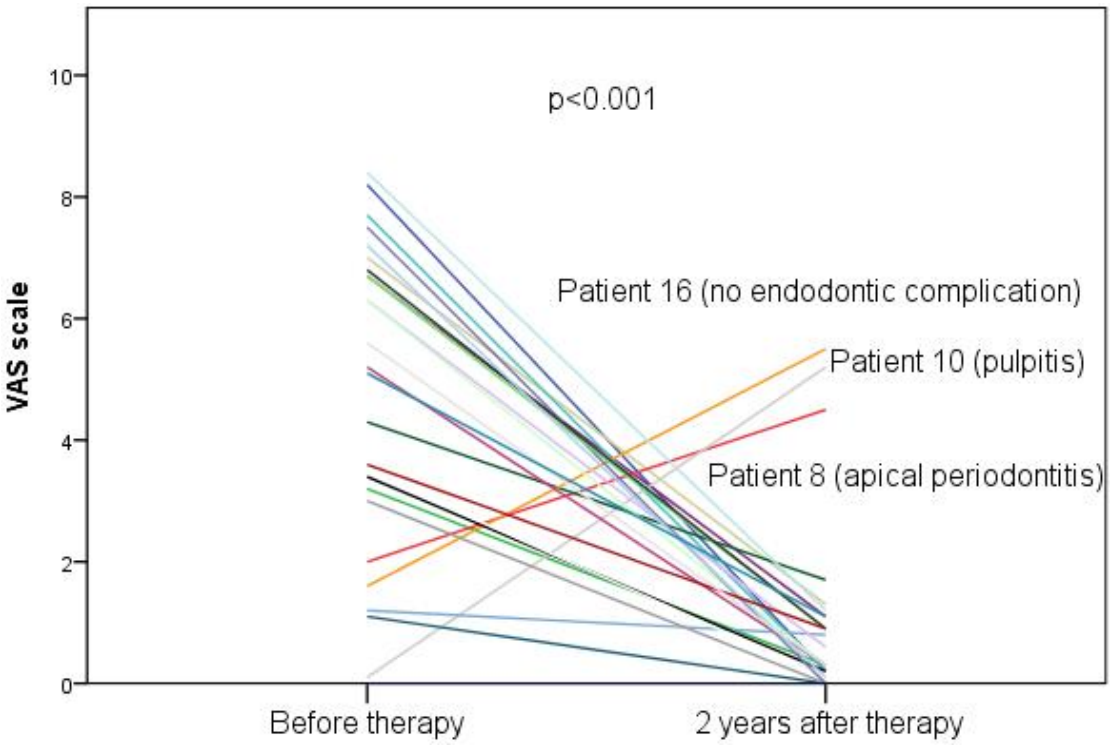


Figure 26. Tooth sensitivity before and 2 y after crown therapy in 27 patients with AI. Visual analogue scale.

Oral health-related quality of life before and after crown therapy (III)

The results of this study show that adolescents and young adults with AI have a worse oral health related quality of life compared to healthy controls. In this section we concentrate on the results from the AI and control groups. The total OHIP-14 score was significantly higher (=worse OHRQoL) among patients with AI (7.0±6.7), compared to the healthy control group (1.4±2.4) (Table 4). Within the different OHIP-14 domains, adolescents in the AI group scored significantly higher on all sub-dimensions of the questionnaire compared to the control group. Items with the highest score among AI patients were orofacial appearance and orofacial pain. Most problems reported in the control group were in orofacial pain.

Two years after crown therapy, OHRQoL improved significantly, total scores decreased from 8.8±5.9 to 2.0±2.5 ($p<0.001$), and the total mean score for all items decreased from 0.6±0.4 to 0.2±0.2 ($p<0.001$). No patient had an increase in total OHIP-14 score after therapy. We found significant improvements in two of four OHIP-14 domains: psychosocial impact and orofacial impact. The study recorded sensitivity of teeth before and after crown therapy using a VAS scale. Before therapy, 19 of 26 patients (73%) reported a VAS score >3 while after crown therapy only three patients (12%) reported a score >3.

We used two different methods to verify if the reduced OHIP-14 score really corresponded to a clinically significant change for the AI patients. The anchor-based method used sensitivity (VAS score <3) as criteria for an important positive treatment effect. The 19 patients who had a VAS score <3 after crown therapy had a mean improvement of five points in their OHIP-14 scores. Nine of 26 patients had a decrease of ≥5 points in their total OHIP-14 score. For the distribution-based method, estimated ES (Cohen's d) for the total OHIP-14 score was 1.24 (95% CI 0.62-1.85). Children with AI did not report a higher level of dental fear using CFSS-DS. Among the various items in the instrument, "injection," "the dentist drilling," and "choking" were the most fearful situations for all groups. Total CFSS-DS scores in patients with AI did not differ before and after crown therapy.

Adolescents and young adults did not have more negative attitudes towards dentistry than healthy controls. Patients with AI scored 32.4±6.4 on the DBS-R, not significantly different from the controls 32.1±5.8 (Table 4). Regarding specific items, all groups mentioned lack of control as a troublesome worry. "When I am in the chair, I don't feel like I can stop the appointment for a rest if I feel the need" was ranked second in the AI group, and third in the

Table. 4 Scores from the oral health impact profile (OHIP-14), the children´s fear survey schedule-dental subscale (CFSS-DS), and the dental belief survey (DBS-R) in the amelogenesis imperfecta (AI), healthy controls (CTR), Molar incisor hypomineralization (MIH) and cleft lip and palate (CLP)

Variables	AI all n=69 x±sd	CTR n=80 x±sd	MIH n=39 x±sd	CLP n=30 x±sd	Significance*
OHIP14 tot sum	7.0±6.7	1,4±2.4	6.8±7.6	13.6±12.1	AI-CTR p<0.001; AI-CLP p=0.034; MIH-CTR p<0.001; CLP-CTR p<0.001; MIH-CLP p=0.037
OHIP 14 mean	3.5±3.4	0.7±1.2	3.5±3.8	7.4±7.6	AI-CTR p<0.001; AI-CLP p=0.033; MIH-CTR p<0.001; CLP-CTR p<0.001; MIH-CLP p=0.029
CFSS-DS	18.8±5.7	18.8±4.6	24.0±8.9	22.1±8.9	AI-MIH p=0.001; AI-CLP p=0.038MIH-CTR p<0.001; CLP-CTR p=0.026
DBS-R	32.4±6.4	32.1±5.8	43.3±20.1	38.6±17.2	AI-MIH p=0.002; AI-CLP p =0.08; MIH-CTR p=0.002; CLP-CTR p =0.033

control group. The total DBS-R score was 31.7±3.9 in the severe AI group before therapy and did not change after therapy, 31.2±4.4. In this group, ranking of the item "I am concerned that the dentist is not really looking out for my best interests" fell from the top concern before therapy to twelfth after therapy.

Adolescents and young adults' experiences of living with AI (IV)

The analysis of the transcribed interviews identified three main themes explaining the experiences of patients living with enamel disturbances caused by AI and receiving early crown therapy. They were: *Disturbances in daily life*, *Managing disturbances*, and *Normalization of daily life*. In these main categories we identified several subthemes (Table 5).

The informants described the insecurity of having teeth prone to disintegration, fractures, and increased sensitivity. Patients discussed their dental fear, not only about visiting the dentist but also of breaking or hurting their teeth. They also disclosed how embarrassing and ashamed they felt showing their teeth and how these feelings preoccupied their time and thoughts.

The patients developed various strategies for avoiding problems and embarrassments. All but one patient mentioned employing strategies to hide or cover their teeth or avoid specific foods when interacting with others. Some patients explained that they felt forced to accept the situation while others were fighting to be listened to. Having support from families, mothers, siblings, and even cousins was a strengthening factor.

Table 5. Themes and subthemes explaining the experiences of patients living with enamel disturbances caused by AI and receiving early crown therapy

Themes	Subthemes
Disturbances in daily life	Dental pain and breakdown
	Embarrassment and shame
	Lack of knowledge and understanding
Managing disturbances	Avoiding, hiding and making excuses
	Resigning or fighting
	Getting support
Normalization of daily life	Reduced pain and eating problems
	Feeling assured and being able to act
	"normally" in relationships
	Being a "normal" dental patient

After crown therapy, all patients reported significantly improved oral health. Not only had their experience of discomfort decreased, but also their esthetic problems. They felt they were treated in a more positive way and also felt and acted differently in a positive way themselves. They also reported that they were treated differently in dentistry after receiving crowns, more professionally and with respect. There was also an end to the problems of having to leave school or a job for dental appointments.

GENERAL DISCUSSION

The four papers included in this thesis show the complexity of problems in patients with AI. Firstly due to biological reasons the quality and longevity of resin composite restorations are poorer compared to restorations placed in individuals with normal enamel. Furthermore the results show that crown therapy performed during adolescence using ceramic materials has excellent long-term performance with few adverse effects. We have also shown that AI has a profound effect on oral health related quality of life and also on activities of daily life. After early crown therapy patients reported a significant improvement in OHRQoL and a normalization of their lives.

Quality and longevity of restorations

The quality of dental restorations in this study was significantly lower in the AI group, with 14% of AI restorations being of excellent quality compared to 51% of control restorations. Normally composite resin restorations show high longevity even in posterior restorations (Da Rosa Rodolpho et al., 2011). Bond strength to the enamel of permanent teeth affected by hypomineralized/hypomatured AI is lower than bond strength to normal enamel. These differences in bonding patterns partly explain the lower quality scores in the AI group. Faria-e-Silva et al. (2011) found a linear relationship between hardness of enamel and bond strength, which may explain the lower survival rates for restorations in patients with the hypomineralized/hypomatured form of AI. It is also possible that sensitivity problems in patients with AI cause dental fear, anxiety, and behavior management problems resulting in sub-optimal conditions for restorative care (McDonald et al., 2012).

The DMFS scores in patients with AI were significantly higher than the scores in age- and gender-matched controls. We analyzed the reasons for performing restorations in both the AI and control groups. Even when only considering dental caries and restorations placed because of dental caries, patients with AI still had significantly higher DMFS scores. Earlier data have suggested higher caries prevalence in patients with AI (Markovic et al., 2010). GBI scores were 50% higher in the AI group compared to controls, which also agrees with previous studies (Coffield et al., 2005; Markovic et al., 2010; Poulsen et al., 2008). Several studies report increased sensitivity in AI affected teeth (Aldred et al., 2003a; Lindunger and Smedberg, 2005;

Poulsen et al., 2008). Our study found significantly higher sensitivity in the AI group using a self-reported VAS that makes comparisons to a control group possible.

Restoration replacement was 2.5 times higher in the AI group than in the control group. In a recent study, dentists reported that time spent on replacement of restorations occupies over 66% of all their operative work with all patients (Forss H, 2011). Because current recommendations for patients with AI suggest use of composites resin restorations, the need for frequent replacements is a problem. Almost two-thirds (63%) of replacements of composite resin-based restorations in AI cases were due to fracture or loss of restorations, while in the control group, recurrent caries caused 35% of the cases and fracture and loss of restorations accounted for only 27%. The high replacement rate in the control group (27% fractures) is because data includes restorations of front teeth subjected to dental trauma.

In patients with AI, the survival rate of composite resin-based restorations after 5 years was approximately 50%, which was significantly lower than the 80% survival rate for the control group. Longevity was worse in younger patients. The longevity of restorations in the control group was similar to previous comparable studies (Kopperud et al., 2012; Vahanikkila et al., 2014).

We found no difference in longevity between glass ionomer and composite resin restorations for patients with AI. For the hypoplastic form of AI, survival of composite resin restorations was significantly higher than for hypomineralized/ hypomatured AI. This is probably due to differences in the bonding and etching patterns between the forms of AI (Faria-e-Silva et al., 2011; Seow and Amaratunge, 1998). In the hypomineralized type of AI, the enamel may be of normal thickness, but it is rough and soft and wears rapidly. In hypomatured AI, the enamel is of normal thickness, but mottled, brownish-yellow, and soft. The prism structure is abnormal and the bonding pattern is insufficient. This contrasts with hypoplastic AI, where the enamel is of normal quality but differs in thickness (Hu et al., 2007). In patients with AI we found no differences regarding longevity of composite resin restorations made before 2009 and those made after. This was probably due to difficulties in bonding to abnormal enamel. We also found a shorter longevity of composite resin restorations in patients diagnosed with severe AI, characterized by extensive enamel breakdown and high sensitivity. In patients with AI, quality and quantity of enamel seem to be more important factors for restoration longevity than recent developments in composite resin materials.

Prosthetic therapy using IPS e.max Press or Procera crowns showed higher survival rates than composite resin restorations in the AI group. Previously high survival rates has been showed

with Procera with zirconia (Zarone et al., 2011). Empress veneers, partial coverage restorations and full crowns had significantly shorter survival rates compared to IPS e.max Press and Procera full crowns with zirconia inner copings.

A randomized controlled trial of crown therapy

The results of the RCT of early crown therapy show that crown therapy can be performed with excellent results in children, adolescents, and young adults with severe forms of amelogenesis imperfecta and that tooth sensitivity was significantly reduced and that adverse events during the 2-year follow-up period were few.

Many authors recommend postponing prosthetic therapy until adulthood (Crawford et al., 2007; Malik et al., 2012; Markovic et al., 2010; McDonald et al., 2012), mostly due to a risk of endodontic complications and the risk for exposure of the disturbing margins of crowns. This study shows that there are many advantages to patients receiving permanent therapy at an early age. Not only can the number of dental appointments and replacements of resin-composite restorations be minimized (Pousette Lundgren and Dahllöf, 2014), but esthetic problems can also be solved and sensitivity problems decreased. It is also possible to use the interdental spaces that exist before mesial movement of the teeth to maintain a normal size for the restored crowns with minimal removal of tooth substance. This may also contribute to an increased quality of life in AI patients since most patients ask for permanent quality restorations at an earlier age (Krieger et al., 2009; Lindunger and Smedberg, 2005).

Longevity of crown therapy is reported to be good (Lindunger and Smedberg, 2005; Pjetursson et al., 2007). A study on patients without AI found loss of vitality followed by caries to be the two most common biological complications (Pjetursson et al., 2007). In AI patients, however, a 10-year follow-up found esthetic problems to be the main reason for crown replacement (Krieger et al., 2009). A 3-year follow-up found that IPS e.max Press crowns demonstrated clinical performance comparable to Procera, AllCeram, and metal-ceramic crowns, while IPS e.max Press performed better with regard to crack propagation and wear resistance in patients without AI (Etman and Woolford, 2010). It seems that new porcelain restoration materials fulfill the demands for quality and longevity, as well as esthetic demands. In our study 97% of crowns were of excellent or acceptable quality after 2 years. We found no differences in longevity or quality between the different groups of AI and no loss of crown. The decreased bonding strength in the hypomineralized/hypomatured

types of AI (Faria-e-Silva et al., 2011), seemed to be of minor importance when using full coverage crowns with mechanical retention.

There are few randomized studies using split mouth design in lateral segments, Federlin et al. (Federlin et al., 2010) found that the 5.5-years survival rate of partial ceramic crowns was 89% compared to 93% in partial cast gold crowns.

Sensitivity was evaluated prior to crown therapy and at the 2-year follow-up. This is one of the important results of this study. The most common problems after ceramic crown therapy in patients without AI is increased sensitivity and gingivitis (Pihlaja et al., 2014). In a randomized controlled study with split-mouth design comparing different cements, Seltz et al. (Selz et al., 2014) found severe hypersensitivity that led to endodontic treatment in 7.4% of abutment teeth in adults without AI. Patients with AI report a high level of tooth sensitivity before treatment. As seen in this study, crown therapy resulted in decreased tooth sensitivity.

Regarding adverse events, we found no difference between the two crown types or between the AI types. A history of dental traumatic injury prior to or after crown therapy seemed to be an important contributing factor to endodontic complications. Endodontic complications appeared in late adolescence, 18 to 19 years of age. It seems that the risk of endodontic problems in young teeth with large pulp chambers is overestimated (McDonald et al., 2012). Out of the 227 teeth in study II, five had an endodontic diagnosis and two were under observation. With seven endodontic complications, the prevalence of endodontic complications was 3% after 2 years. The estimated rate of loss of vitality in adult patients without AI after crown therapy is 6.1% (4.9–7.6%).

Oral health related quality of life

Adolescents and young adults with AI reported a significantly lower OHRQoL compared to healthy controls and therapy with porcelain crowns significantly improved OHRQoL.

Many dental conditions have psychological and social implications; thus, patient reported outcomes should supplement specific dental outcome measures (Gilchrist et al., 2014). In this study, patient age varied between 6 and 25 years. Although the OHIP-14 has not been validated in younger children (Jokovic et al., 2002), we decided to use this scale, because the majority were teenagers and young adults. And although the 49 items of the OHIP-49 are reduced to 14 in the OHIP-14, it shows good statistical properties and validity (Slade, 1997). Internal

reliability (Crohnbach's α) of the OHIP-14 items in this population aged between 6 and 25 years was 0.886. The individual items varied between 0.869 and 0.892.

The negative esthetic experience from tooth discoloration and reduced crown size in patients with AI leads to higher levels of social avoidance and distress than subjects without the condition (Aldred et al., 2003a). Patients diagnosed with AI are more often single compared to controls and have fewer children (Coffield et al., 2005). In this study, children with AI reported a significantly lower OHRQoL compared to healthy controls. This agrees with two previous studies of adult patients with AI (Coffield et al., 2005; Hashem et al., 2013). The mean total OHIP-14 score in the study of AI patients with a mean age of 36 years was 25 (Coffield et al., 2005), compared to a mean score of 7 in our group of patients with a mean age of 15. This can be explained by the many years of living with an esthetically suboptimal dentition, increased sensitivity, and frequent dental visits for replacement of restorations (Pousette Lundgren and Dahllof, 2014).

Minimally important difference is an important concept when interpreting results from longitudinal studies of the effects of dental treatment on OHRQoL. It is usually defined as the smallest difference in score that patients perceive as beneficial, and which would mandate a change in patient management in the absence of troublesome side effects and costs (Jaeschke et al., 1989). The results clearly show a significant positive effect on OHRQoL for crown therapy in patients with AI. The OHIP-14 score reduced significantly compared to controls, and none of the patients reported a worsening score. A reduction in VAS pain score below 3, which indicates no pain or low pain that does not require analgesics (van Dijk et al., 2002), was our standard for determining a clinically important difference in OHRQoL. We found that the OHIP-14 scores of patients who reported a VAS pain score below 3 decreased by 5 points after therapy and that nine patients of 26 (35%) had a ≥5-point reduction. This is similar to the minimally important difference for OHIP-14 reported in a study of adult patients receiving periodontal therapy, which reported a 5-point decrease for a third of the patients (Tsakos et al., 2010). In this study, the ES (Cohen's *d*) for within-group comparisons was 1.24, which is a very large treatment effect (Cohen, 1990). None of the patients with AI who received crown therapy reported a worsening OHRQoL, which is an important aspect of their responsiveness to treatment that adds strength to the results (Revicki et al., 2006).

Patients with AI did not express negative attitudes towards dental treatment, either before or after crown therapy. Both patients with AI and controls scored lower than a comparable group of Swedish patients (Abrahamsson et al., 2006). Among the concerns that they reported, lack of control and the need to be listened to when reporting pain were highly ranked. Before

treatment, the severe AI group scored the item “I am concerned that the dentist is not really looking out for my best interests” as their top concern. After therapy this item fell to rank 12 of 28 items.

Experiences of living with AI

The qualitative study showed the profound impacts on daily life experienced by children and adolescents affected with AI. The results give voice to these individuals and provide insight into what it means to live with AI when growing up. These results supplement our previous study showing a reduced OHRQoL in children and adolescents with AI (Pousette Lundgren et al., 2015). Marshman et al., (2007) pointed out that, while most studies use children as objects of research, few studies focus on children’s own views of their treatment (Marshman et al., 2007).

This study identified three major themes: *Disturbances in daily life*, *Managing disturbances*, and *Normalization of daily life*. In the patients’ own voices, the themes describe the impact of AI on their daily life, how they cope with the consequences of the condition, and how early treatment with porcelain crowns changed their daily life.

Accumulating evidence is showing that patients with AI experience lower OHRQoL than patients without AI (Coffield et al., 2005; Hashem et al., 2013; Pousette Lundgren et al., 2015). Bio-psychosocial factors explain the determinants of OHRQoL; these include symptoms, functional status, and general health perceptions within the context of individual and environmental characteristics (Broder et al., 2014).

Patients in this study reported heightened tooth sensitivity with painful experiences when eating or drinking warm or cold foods or drinks, or when going out into cold weather. They also reported pain reactions to restorative materials and more painful dental treatments without sufficient local anesthesia. The results are in line with a previous study by Coffield et al. (2005) in which 82% of AI patients reported increased sensitivity compared with a control group (Coffield et al., 2005). The results also showed that these painful stimuli can be unpredictable and that pain can occur a day after exposure.

All patients in this study expressed concerns about the appearance of their teeth and that they felt different in a negative way. They also said that the condition affected them in a negative way in daily life. They were preoccupied with thoughts about how the appearance of their teeth would affect people they met and what these people would think of them.

Appearance becomes more important during adolescence. There are strong cultural pressures to conform to beauty ideals, and adolescents often become preoccupied with their own and others' appearance (Brown and Witherspoon, 2002). Children with visible differences have been found to be more likely to encounter discrimination and unsolicited negative attention from others (Griffiths et al., 2012). Fractures and loss of restorations resulted in many dental appointments that also affected school performance. Being questioned regarding the necessity for frequent dental appointments, often in front of others, was a burden for the patients.

AI is a rare disorder, and general dentists, hygienists, and dental assistants do not often meet patients with AI. Children and adolescents in this study describe a variety of problems with dental staff that either did not understand their condition and its consequences and blamed them for poor oral hygiene or did not understand their need for extra pain relief. Klingberg et al. (2012) reported similar results in children with rare disorders, physical disabilities, and cognitive impairments where lack of knowledge, lack of understanding of patient needs, and lack of organizational support negatively affected quality of care (Klingberg and Hallberg, 2012). In order for dentists to provide successful care in situations that deviate from the norm requires them to handle professional uncertainty, to dare to face difficulties, and to work in a tolerant work environment (Hallberg et al., 2004). Patients in this study also reported that dentists did not listen to them and their specific problems. Reports show that dental professionals try to normalize children with rare disorders in order to make their treatment situation more manageable (Hallberg et al., 2004).

Patients interviewed in this study reported several strategies to avoid the pain and increased sensitivity caused by AI, including hiding their condition from others and avoiding social situations where they risked unsolicited comments from others. Fear of negative judgments and social anxiety can result in social avoidance and interpersonal difficulties, which may impede the development of social skills and lead to isolation from peers (Chamlin, 2006). Adult patients with AI reported higher scores on social avoidance and distress compared to those without the condition. They also reported higher fear of negative evaluation by others and lower self-esteem and mastery (Coffield et al., 2005).

The daily experiences of AI patients reported in this study are the consequence of current treatment paradigms (Chen et al., 2013; McDonald et al., 2012). Patients have been told that there is nothing to do except wait until adulthood and manage with temporary restorations in the meantime. Some patients responded to this with resignation; others, especially those who had parents, siblings, or cousins with the same condition, had the knowledge and power to fight for adequate treatment. This is a common situation for parents of children with disabilities,

having to fight for their child's right to treatment (Trulsson and Klingberg, 2003). It is also evident that treatment and education from the specialist pediatric dentistry clinic empowered the patients with knowledge and a permanent definitive treatment.

After crown therapy, pain and sensitivity problems decreased and it was possible to live without pain. Several patients said that, for the first time, they realized how much pain they had had and how it had affected their lives. After crown therapy, all patients reported that they were relieved and did not constantly think about how their teeth would appear to others. Patients received positive remarks from others, felt proud of their teeth, and became happier people, smiling and laughing more. Treatment also resulted in increased autonomy for the patients. Now they could eat and drink everything and at the same speed as their friends. Issues with their teeth changed from being a constantly present problem to no problem at all. Feeling like a normal, intact person strengthened the self-confidence of all patients.

Regarding the timing of crown therapy, most patients thought it should have been done at an earlier age. The patients suggested that if crown therapy began at 12 years of age, even if they were subjected to extensive prosthetic rehabilitation, it would all be worthwhile. The results underline the importance of listening and giving a voice to the child as an acting subject capable of speaking about his or her own health.

Reflections on crown therapy in patients with AI

After information about possibilities and risks with early crown therapy, the patient had to think over the offered treatment plan during three months and discus with parents if under 18 years of age. Pre-prosthetic orthodontic therapy was performed if necessary with the aim to retain interdental spaces and optimize possibilities for a favorable occlusal curve. During this period appointments were focused on optimizing oral hygiene, and if necessary to introduce local anesthesia. This part of the treatment was performed in cooperation with dental hygienists. After this waiting period, patients and parents were asked to make the decision to start therapy or not. The patient's ability to cooperate during treatment was evaluated and efforts were made to confirm that the patient expressed the treatment needs himself or herself. If the demands came from parents and we found the patient being doubtful we advised to postpone the treatment.

The tooth eruption pattern decides when crown therapy can be performed in a growing individual. Treatment was most commonly started with maxillary incisors. It was for the patient

to decide which teeth to restore and where to start depending on problems in the individual case. They also had to decide during the whole rehabilitation process if they still wanted to continue with more crown therapy.

Nitrous oxygen sedation was offered to all patients and analgesics before (paracetamol) and after treatment (ibuprofen) was recommended to all patients to reduce pain during and after treatment. Paracetamol in combination with codeine is reported as effective analgesics in postoperative treatment. As the codeine adds only 10% effect and have adverse effects we used paracetamol without codeine (Toms et al., 2009). It has been concluded that even brief intervals of acute pain can induce long-term neuronal remodeling and sensitization ("plasticity"), chronic pain, and lasting psychological distress (Carr and Goudas, 1999).

Topical lidocaine was used before local anesthesia was applied. Having effective local anesthesia during the treatment is important. All patients were asked to report pain during therapy using a visual analogue scale and if necessary local anesthesia was supplemented. No crown had to be remade due to poor fit at cementation, probably because we had cooperation from informed patients, no problems with gingival bleeding. A stopwatch was used to let the impression material set for exactly six minutes. If there were any doubts regarding the quality of the impression, a new one was immediately made. During cementation of the crowns the same procedure with sedation, analgesics and local anesthesia was used. In the front regions 2 to 6 teeth were made at the same time while in the lateral segments one to three teeth were made at the same visit.

Current ceramic material allows thin restorations and minimal preparation. Particularly IPS e.max Press crowns reduce the amount of tooth substance that has to be removed in comparison to metal-ceramic combinations. Using interdental spaces before the mesial movement of the teeth, the reduction in tooth substance could be even less, especially in patients with thin enamel. This additional tooth substance, in combination with young teeth that have good blood supply and wide apices, could be the reason that few endodontic complications have occurred (Andreasen et al., 2012; Olsburgh et al., 2002). Therefore we can recommend preparation for crowns with minimal invasive techniques.

We acknowledge the benefit of having a patient feeling comfortable and secure during treatment process. Contributing to this is an individual therapy plan, which has been found important in previous studies (Koruyucu et al., 2014). In many cases we had preferred to meet the patients at an earlier stage to make an early diagnosis and therapy plan as recommended (Markovic et al., 2010; McDonald et al., 2012).

Methodological considerations

The present study includes several different research designs. The first study includes both a cross-sectional study of restoration quality and a retrospective study of restoration longevity from dental records. The second study is a randomized controlled trial of two different ceramic crown materials with a two-year follow-up period. The third is a cross-sectional study and use questionnaires to study OHRQoL. The change in studied parameters was followed for two years in patients with severe AI. Finally, the fourth study is a qualitative interview study using thematic analysis to complement results from the study of OHRQoL.

Regarding the first study, given the low prevalence of AI, it would be difficult to include a sufficient number of patients in a prospective, randomized study of the current treatment protocol. It would be unethical to place composite resin restorations of an inferior quality to patients with AI in such a study. The retrospective study had the usual limitations, such as the fact that many of the dentists performed both the diagnosis of dental caries as well as the restorative treatment, and that there was no diagnostic calibration prior to this study. Another limitation was the low number of restorations in the control group.

A randomized controlled trial (RCT) was included in this thesis. The trial was registered at www.controlled-trials.com: ISRCTN70438627. RCT makes it possible to make causal interference and gives the strongest evidence of treatment efficacy. In this study we compared two ceramic crown materials since it was not possible to compare with standard therapy as it has inferior quality. Our study used a split-mouth method for the lateral segments while using one material for the whole front segments. There were no significant differences in quality of crowns between the crown types in the strict split-mouth selection and between teeth without a corresponding tooth or teeth in the frontal segments. For esthetic reasons, it is not possible to use a split-mouth design for the frontal region (Pjetursson et al., 2007). The results must be interpreted with caution since two years may be too short to document all late complications in a group of growing individuals.

The study on OHRQoL had some limitations due to the higher dropout rate in the CLP and MIH groups. These patients were identified through patient administrative records and could not be reached personally. Another limitation was the advice to the PDS clinics not to make composite resin restorations before expected crown therapy in patients with AI. Limitations related to questionnaires include that the questions are fixed and thus may not capture the children's own experiences of their disease. Strengths of this study include that it studied OHRQoL after treatment and that it estimated the clinically meaningful effect.

In the qualitative study we used thematic analysis to study experiences and perceptions of children and adolescents with AI. We used a convenience sample of patients living close to two major cities in Dalarna. Strengths of the study include that all the patients we asked agreed to participate. Second, an experienced psychologist conducted the interviews and the transcripts show that it is the voices of the patients that are the material for analysis. We have also been able to triangulate the results with quantitative data from two other studies in this project regarding pain and sensitivity and the effect of crown therapy on OHRQoL.

Ethical reflection

In the UN convention on the rights of the child a founding principle is "Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States shall strive to ensure that no child is deprived of his or her right of access to such health care services". Children with AI were are reported to have serious dental health problems and poor quality of life. The aim of this project was to develop treatment methods that more rapidly could lead to a normalization of their daily lives.

For research to be ethical, it must be of such a standard and be conducted in a way that will generate new and useful knowledge. Therefore, we aimed at a randomized controlled trial of a new treatment that would be beneficial to young patients with AI and an appropriate follow-up period that made it possible to draw definitive conclusions.

Children and young individuals have limited capacity for understanding and may be more open to coercion and can be regarded as a more vulnerable population. In addition to dental problems AI also have psychological impact, as there is a strong emphasis being esthetically attractive in modern society. We have tried to respect the participating individuals own will by involving them in the decision process regarding their therapy and to give them time to make an informed decision. The emphasis of the treatment is on restoring function and decreasing symptoms, improved esthetics is a secondary aim.

As alluded to before most research is conducted on children and use end-points decided by the profession. In research, participants must have the power to make their own decisions. This means respect for the individual, their thoughts, beliefs and wishes regarding the treatment. Also to respect their need for privacy and confidentiality. In this project we have combined dental outcome measures with quality of life measures and also tried to give voice to the participants describing how they experience living with AI and receiving dental treatment.

In these studies, we have obtained both parental consent and child assent. If the parent asked for therapy for his or her child, and child was hesitant, treatment was postponed one year to ensure that the child's own will was respected.

Crown therapy in children with AI may be burdensome because of the increased sensitivity, difficulties with local anesthesia, long treatment sessions and treatment over many years. Our clinical experience was that the possible benefits of crown therapy outweighed the possible harms. There is also a risk of adverse events with crown therapy. When dealing with children and adolescents the acceptable level of risk should be lower compared to when treating adult patients. Also regarding risk, the possible benefits outweighed the risks. We also ensure a strict follow-up program after treatment.

MAIN FINDINGS AND CONCLUSIONS

Study I

Quality of composite resin and glass ionomer restorations in patients with AI was worse than for normal controls. The longevity of composite resin restorations in patients with AI was shorter than for controls and that prosthetic crown therapy had significantly better longevity than both resin composite and glass ionomer restorations in the AI group. Resin composite restorations had a shorter longevity for hypomineralized/hypomatured AI than for hypoplastic AI.

Study II

After two years, 97% of the crowns in both crown groups had excellent or acceptable quality. We found no significant differences between Procera and IPS e.max Press crowns with regard to quality and longevity. Crown therapy also resulted in decreased sensitivity problems in young AI patients. It seems to be possible to perform early crown therapy without severe complications in young patients with AI.

Study III

Patients with AI rated their OHRQoL significantly lower than healthy controls. OHRQoL improved significantly in these patients after crown therapy. Furthermore, the treatment effect was clinically significant. Extensive dental therapy did not increase dental fear or negative attitudes towards dentistry.

Study IV

Adolescents and young adults describe a profound effect of AI on several aspects of their daily life. Experiences include severe pain and sensitivity problems, feelings of embarrassment, and dealing with dental staff that lack knowledge and understanding of their condition. Furthermore, the patients described ways to manage their disturbances and to reduce pain when eating or drinking, and strategies for meeting other people. After definitive treatment with porcelain crown therapy, they described feeling like a “normal” patient.

CLINICAL IMPLICATIONS

The results showed an inferior quality of particularly resin composite restorations in patients with AI. It is important to aim for restorations with longer survival. Since the enamel quality is inferior, materials not depending on bonding systems are preferable. In a situation where resin composite restorations fail or extensive areas of the tooth affected, is it particularly important to look for alternatives. Glass ionomer can be used as an alternative during eruption of teeth. As soon as the tooth is erupted crown therapy with new ceramic materials should be considered.

Patients with AI complained of high sensitivity in teeth as evaluated by a visual analogue scale. It is evident that pain experienced by patients should be measured and also documented. A visual analogue scale is suitable for this. When deciding on restorative material, the effects on sensitivity should be taken into account. We have shown that crown therapy significantly reduces pain and sensitivity in teeth affected by AI.

Pain free dental treatment is a goal for all patients in dentistry. In AI patients this needs particular attention. First, all patients should be offered analgesic drugs before and the same day after treatment. Paracetamol and ibuprofen can be used also in combination. Topical anesthesia with lidocaine should be offered prior to injection. Use of local anesthesia, with supplemental doses if necessary is mandatory. When working in one segment of the jaws it is advisable to cover teeth in other segments using fluoride varnish or dental impression material to minimize the risk of pain from air or water.

Patients with AI also had higher caries prevalence compared to controls even when fractures were omitted from DFMS. This indicates a higher caries risk and a preventive program based on fluorides should be introduced. Support with oral hygiene is also indicated since many patients with AI have enamel with a rougher or pitted surface that are more prone to plaque retention and gingivitis

The randomized controlled trial showed that porcelain crown therapy performed from adolescence have excellent two-year survival, and even five-year follow-up with a low rate of adverse effects. This indicates that crown therapy may be an alternative in cases with severe AI. Factors to be taken into account are sensitivity problems, wear, enamel breakdown and also esthetics. If crown therapy is performed in early teenage period, interdental spaces can be utilized; requiring less preparation of AI affected teeth.

It is notable that the often extensive and time consuming prosthetic therapy given to AI patients did not cause an increase in dental anxiety or cause more negative attitudes towards dentistry.

With regard to follow-up of performed crown therapy and endodontic complications, dental trauma seems to be an important risk factor. The question of visible crown margins did not seem to be a problem among this group of AI patients, elongation of teeth were only seen in patients with long face growth pattern.

Patients with AI reported a lower oral health related quality of life and significant improvement after crown therapy. It is evident that orofacial appearance and orofacial pain are factors that need to be addressed and taken into account in the treatment plan.

Patients with AI reported that the condition had a significant impact on their daily lives. When meeting patients with AI it is important to listen to how they describe their situation and how it affects them. Dental professionals should focus on how AI affects patients daily life, on sensitivity and pain, if they feel embarrassed or shame and how they manage the problems when eating and drinking and in social situations.

From the qualitative study it is evident that patients with AI were met with lack of knowledge, lack of understanding of their situation in dental care. Important is to offer enough time to listen and examine the patient, to respect their views and to offer the prospect of a treatment that can solve their problems. Continuing education on rare conditions is important as well early referral if the situation cannot be handled in general dentistry.

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